Tab A

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 5, 206, 250, 314, 600, and 601

[Docket No. 1999N–0193]

RIN 0910–AB61

Supplements and Other Changes to an Approved Application

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending its regulations on supplements and other changes to an approved application to implement the manufacturing changes provision of the Food and Drug Administration Modernization Act of 1997 (the Modernization Act). The final rule requires manufacturers to assess the effects of manufacturing changes on the identity, strength, quality, purity, and potency of a drug or biological product as those factors relate to the safety or effectiveness of the product. The final rule sets forth requirements for changes requiring supplement submission and approval before the distribution of the product made using the change, changes requiring supplement submission at least 30 days prior to the distribution of the product, changes requiring supplement submission at the time of distribution, and changes to be described in an annual report.

DATES: This rule is effective [*insert date 75 days after date of publication in the* **Federal Register**]. ~~Written comments on the information collection requirements should be submitted by [*insert date 30 days after date of publication in the* **Federal Register**].~~

JMB

ADDRESSES: The Office of Management and Budget (OMB) is still experiencing significant delays in the regular mail, including first class and express mail, and messenger deliveries are not being accepted. To ensure that comments on the information collection are received, OMB recommends that written comments be faxed to the Office of Information and Regulatory Affairs, OMB, Attn: Fumie Yokota, Desk Officer for FDA, FAX: 202-395-6974.

✓ OMB

FOR FURTHER INFORMATION CONTACT: Nancy B. Sager, Center for Drug Evaluation and Research (HFD–357), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–5633, or Robert A. Yetter, Center for Biologics Evaluation and Research (HFM–10), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852, 301–827–0373.

SUPPLEMENTARY INFORMATION:

I. Background

Section 116 of the Modernization Act (Public Law 105–115) amended the Federal Food, Drug, and Cosmetic Act (the act) by adding section 506A (21 U.S.C. 356a). That section describes requirements and procedures for making and reporting manufacturing changes to approved new drug and abbreviated new drug applications, to new and abbreviated animal drug applications, and to license applications for biological products under section 351 of the Public Health Service (PHS) Act (the PHS act). Section 506A of the act revises current procedures for approving manufacturing changes. Major manufacturing changes, as defined in section 506A of the act, are of a type determined by the Secretary of Health and Human Services (the Secretary) to have a substantial potential to adversely affect the identity, strength, quality, purity, and potency as they may relate to the safety and effectiveness of a drug. Such changes require prior approval of a supplemental application. Section 506A

of the act also states that the Secretary may require submission of a supplemental application for drugs made with manufacturing changes that are not major and may establish categories of manufacturing changes for which a supplemental application is required. In such a case, the applicant may begin distribution of a drug 30 days after FDA has received a supplemental application unless the agency notifies the applicant within the 30-day period that prior approval of the application is required. Under the statute, FDA may also designate a category of manufacturing changes that permit the applicant to begin distributing a drug made with such changes upon receipt by the agency of a supplemental application for the change. Finally, FDA may also authorize applicants to distribute drugs manufactured with a change without submitting a supplemental application. The law provides that FDA may establish categories of manufacturing changes that may be made without submitting a supplemental application.

A. Development of the Regulation

In the **Federal Register** of June 28, 1999 (64 FR 34608), FDA published a proposed rule to implement section 506A of the act for human new drug applications (NDAs) and abbreviated new drug applications (ANDAs), as well as for licensed biological products (the June 1999 proposal). In that same issue of the **Federal Register** (64 FR 34660), FDA announced the availability of a draft guidance for industry entitled "Changes to an Approved NDA or ANDA." This guidance was intended to assist applicants in determining how they should report changes to an approved NDA or ANDA under section 506A of the act as well as under the proposed revisions to the human drug regulations pertaining to supplements and other changes to an approved application. In the **Federal Register** of November 23, 1999 (64 FR 65716), FDA announced

the availability of a guidance to assist applicants in determining how they should report changes to an approved NDA or ANDA under section 506A of the act, pending finalization of the June 1999 proposal. FDA has revised the guidance to conform to this final rule and is announcing the availability of the guidance elsewhere in this issue of the **Federal Register**.

B. A Risk-Based Approach

The publication of this final rule is an important step in the process of adopting a risk-based approach to the regulation of pharmaceuticals. In the 1990s, FDA sponsored research at the University of Maryland and other universities on the types of chemistry and manufacturing changes to immediate release solid oral drug products that could affect drug performance (i.e., identity, strength, quality, purity, and potency) and, therefore, safety and effectiveness. Using that research, FDA's Center for Drug Evaluation and Research (CDER) began to develop a risk-based approach to the implementation of manufacturing changes. The approach provided for a continued high level of scrutiny by FDA of changes that were most likely to affect the performance of a drug and decreased scrutiny of changes that were not likely to affect the performance of a drug.

The risk-based approach was first explained in a series of guidance documents (the Scale-up and Postapproval Changes (SUPAC) guidances) that reduced the regulatory burden of obtaining FDA authorization to make certain changes. The work continued in regulations issued by the Center for Biologics Evaluation and Research (CBER) in 1997 (21 CFR 601.12). In November 1997, this risk-based approach was codified in section 116 of the Modernization Act.

This final rule implements section 116 of the Modernization Act by incorporating the statutory standards for characterizing proposed changes as

having substantial, moderate, or minimal potential to adversely affect the identity, strength, quality, purity, and potency of a drug as they may relate to its safety and effectiveness and determining submission requirements based on the potential risks associated with the changes. For changes with a substantial potential to affect the designated characteristics of a drug, FDA must review and approve a supplement that contains information showing that the proposed change will not adversely affect the drug's characteristics (i.e., information developed by the holder of the application to validate the effect of the proposed change) before distribution of the product made using the change.

It was anticipated when section 116 of the Modernization Act was written that the science of manufacturing would evolve over time and affect whether changes would be considered major or nonmajor. To accommodate future technological advancements, section 116 of the Modernization Act and this final implementing regulation both provide that FDA may, by regulation or guidance, change the designation of a particular category of change from major to nonmajor or vice versa. This concept of an evolving risk-based approach to manufacturing changes also is consistent with the agency's Good Manufacturing Practices Initiative ("Pharmaceutical cGMPs for the 21st Century," *www.fda.gov/cder/gmp/index.htm*). The goals of that initiative, launched in August 2002, include:

- Ensuring that state-of-the-art pharmaceutical science is utilized in the regulatory review and inspection policies;

- Encouraging the adoption of new technological advances in high quality and efficient manufacturing by the pharmaceutical industry;

• Assessing the applicable current good manufacturing practice (CGMP) requirements relative to the best quality management practices;

• Strengthening public health protection by implementing risk-based approaches that focus both industry and FDA attention on critical areas for improving product safety and quality; and

• Enhancing the consistency and coordination of FDA's drug quality oversight activities.

Specifically, one of the efforts of the CGMP initiative is to facilitate continuous improvement and innovation in manufacturing by allowing manufacturers to make certain types of changes in their processes without prior FDA approval. This rule, in keeping with that initiative, provides for a mechanism of continuous improvement through the guidance process (21 CFR 10.115) that may provide for less burdensome documentation of certain changes as manufacturing processes and pharmaceutical science develop.

II. Highlights of Revisions to the Proposed Rule

A. Definitions

FDA has revised the proposed definition of "specification" by changing the phrase "other components including container closure systems and in-process materials" to "components, in-process materials, container closure systems, and other materials used in the production of a drug substance or drug product." FDA made this change for consistency with other regulations. FDA proposed a definition for the term "validate the effects of the change." In the final rule, the agency has changed the word "validate" to "assess" and provides a definition for the term "assess the effects of the change."

B. Changes to an Approved Application

The proposal required that the holder of an approved application validate the effects of manufacturing changes on the identity, strength, quality, purity, and potency of the drug as these factors may relate to the safety or effectiveness of the drug. FDA has revised this provision to require that the holder of an approved application assess the effects of manufacturing changes. FDA has deleted the phrase "on the identity, strength, quality, purity, and potency of the drug product as these factors may relate to the safety or effectiveness of the drug product" because this information is already included in the definition of the term "assess the effects of the change."

Previously, § 314.70(c) (21 CFR 314.70(c)) stated that the applicant who submits a changes-being-effected supplement to FDA must promptly revise all promotional labeling and advertising to make it consistent with any change in the labeling. The proposal retained this provision and FDA stated in the preamble that the requirement would apply equally to all labeling changes. FDA has revised this provision to limit the requirement to those labeling changes submitted in supplemental applications and not to those in annual reports.

The proposal required the applicant to include in a cover letter a list of all changes contained in the supplement or annual report. FDA has clarified that the requirement to include the list of changes in a cover letter applies only to changes contained in a supplement; the information is already submitted in an annual report.

C. Changes Requiring Supplement Submission and Approval Prior to Distribution of the Product Made Using the Change (Major Changes)

FDA has limited the requirement to include only those changes to a drug product container closure system that involve changes in the type or composition of a packaging component. FDA intends to provide additional guidance on container closure systems changes that will be considered moderate changes or changes that can be reported in an annual report.

FDA proposed to require that a reference list of relevant standard operating procedures (SOPs) be contained in all supplements submitted under this section. FDA has revised this provision to specify that a reference list of relevant SOPs must be submitted for changes to a natural product, a recombinant deoxyribonucleic acid (DNA)-derived protein/polypeptide product, or a complex or conjugate of a drug substance with a monoclonal antibody, and for changes to the sterilization process and test methodologies related to sterilization process validation.

D. Changes Requiring Supplement Submission at Least 30 Days Prior to Distribution of the Drug Product Made Using the Change (Moderate Changes)

FDA has revised the June 1999 proposal to clarify that the requirement to submit 12 copies of finished product labeling applies to supplements for changes that may be implemented 30 days after FDA receives the supplement.

FDA has clarified that the changes in the container closure system submitted in supplements under these moderate changes provisions do not include the changes described under the provisions requiring prior approval or the changes submitted in an annual report.

FDA has revised the changes solely affecting a natural protein product, a recombinant DNA-derived protein/polypeptide product, or a complex or

conjugate of a drug with a monoclonal antibody to specify the use of "different equipment" instead of "new or different equipment" for changes in production scale, and equipment of "a different design" instead of "similar but not identical design and operating principle" for the replacement of equipment.

FDA is also adding to the moderate changes provisions a change in the relaxation of an acceptance criterion or deletion of a test to comply with an official compendium that is consistent with FDA statutory and regulatory requirements. FDA is not requiring that a prior approval supplement be submitted for this type of change because the change has been reviewed by the United States Pharmacopeia (USP), and FDA and the public have had an opportunity to review, in general, the change through the USP process. However, because FDA will not have reviewed such a change in the context of each individual application affected by the change, a changes-being-effected-in–30–days supplement will still be required.

FDA has revised the proposal to clarify that the applicant may not distribute the drug product until the supplement for a change under this provision has been amended to provide missing information that has been requested by FDA.

E. Changes That May Be Implemented When FDA Receives a Supplement (Moderate Changes)

FDA has clarified that labeling changes that normally require a prior approval supplement may, at the agency's request, be implemented when FDA receives a supplement.

F. Changes To Be Described in the Next Annual Report

FDA has revised the June 1999 proposal to state that any change made to comply with an official compendium that is consistent with FDA statutory

and regulatory requirements may be submitted in the next annual report, except a change involving the relaxation of an acceptance criterion or deletion of a test to comply with an official compendium.

FDA has revised the June 1999 proposal to clarify that the majority of changes concerning replacement of equipment with equipment of the same design and operating principles may be submitted in an annual report. However, there are certain equipment changes identified in this rule that require submission in a changes-being-effected-in-30-days supplement or a changes-being-effected supplement.

FDA has revised the June 1999 proposal to clarify that certain changes made to the container closure systems for sterile drug products may be submitted in annual reports, as may certain changes for nonsterile drug product container closure systems. The changes are those based on a showing of equivalency under an approved or official compendium protocol.

FDA has revised the June 1999 proposal to clarify that an extension of an expiration dating period that can be reported in an annual report can be based on production batches instead of full production batches. FDA considers a production batch to be one made at production scale using production equipment in a production facility as specified in the application. Production scale does not necessarily mean the largest batch size produced, but a batch of a size or within a batch size range that has been approved in the application.

FDA has deleted the requirement that an annual report contain a list of all products involved in the changes. FDA has also clarified that an annual report must include the date each change was implemented instead of the date each change was made. FDA considers "the date each change was implemented" to be the date that the condition established in the approved

application is changed, not when the product made with the change is distributed. FDA has also revised the June 1999 proposal to clarify when validation protocols and SOPs must be included in an annual report submission.

G. Other Information

FDA has revised the June 1999 proposal to clarify that a protocol must be submitted as a prior approval supplement if the protocol was not already included in an approved application or when changing an approved protocol. In the June 1999 proposal, FDA used the terms "drug," "drug product," "drug substance," and "product." The agency has standardized the terminology throughout the final rule and used the terms "drug product," "drug substance," and/or "product" as appropriate. In addition, the agency has made minor edits to the final rule in response to former President Clinton's June 1, 1998, memo on plain language in Government writing.

III. Responses to Comments on the June 1999 Proposal

FDA received comments on most aspects of the June 1999 proposal from more than 30 pharmaceutical companies, pharmaceutical industry associations, and other interested persons. The comments and the agency's responses follow.

A. General Comments

(Comment 1) Many comments said the June 1999 proposal does not meet the intent of Congress when establishing section 506A of the act. The comments said that Congress expected the following: (1) Significant changes in FDA's past practices on manufacturing changes; (2) substantial improvement in the management of technical supplements for manufacturing changes; (3) regulatory relief without compromising quality, safety, or efficacy of drugs; (4)

appropriate action on the marketing of regulated products in a manner that does not unduly impede innovation or product availability; (5) reduction in reporting and regulatory requirements; and (6) a small number of major manufacturing changes that require prior approval, but that most changes would require a less burdensome means of reporting than has been required in the past. Several comments said the June 1999 proposal generates new requirements for making regulatory submissions, adds new categories for making those submissions, and increases the documentation burden on industry. One comment also noted that the SUPAC guidances[1] would not fulfill the Congressional intent because they were published before the Modernization Act.

FDA believes that these regulations are consistent with the intent of Congress and that the regulatory requirements and reporting categories are consistent with section 506A of the act. Section 506A of the act provides FDA with considerable flexibility to determine the information and filing mechanism required for the agency to assess the effect of manufacturing changes in the safety and effectiveness of the product. There is a corresponding need to retain such flexibility in the proposed regulations implementing section 506A of the act to ensure that the least burdensome means for reporting changes are available. FDA believes that such flexibility will allow it to be responsive to increasing knowledge of and experience with certain types of changes and help ensure the efficacy and safety of the products involved. For example, a change that may currently be considered to have a substantial potential to have an adverse effect on the safety or effectiveness of the product

[1] As explained in the June 1999 proposal, FDA developed the SUPAC guidances to ease preapproval requirements by categorizing certain manufacturing changes according to whether they had a minor, moderate, or major potential to affect product quality and performance.

may, at a later date, based on new information or advances in technology, be determined to have a lesser potential to have such an adverse effect. Conversely, a change originally considered to have a minimal or moderate potential to have an adverse effect on the safety or effectiveness of the product may later, as a result of new information, be found to have an increased, substantial potential to adversely effect the product.

The agency believes it can more readily respond to knowledge gained from manufacturing experience, further research and data collection, and advances in technology by issuing regulations that set out broad, general categories of manufacturing changes and by using guidance documents to provide FDA's current thinking on the specific changes that fall into those general categories. The regulations provide for a new approach to regulating postapproval manufacturing changes. The approach is based on the potential for a change to adversely affect the identity, strength, quality, purity, or potency of drug products as these factors relate to the safety and effectiveness of the product. The regulations and companion guidance "Changes to an Approved NDA or ANDA" will provide significant regulatory relief by allowing postapproval manufacturing changes to be implemented more rapidly, while still ensuring the identity, strength, quality, purity, and potency of drug products.

The regulation reduces the overall number of supplements requiring FDA approval prior to product distribution. In addition, many changes that are currently reported in supplements would be reported in annual reports. The regulation will not increase the number of annual reports but will allow applicants to include in an annual report information currently required to be reported to the agency in a supplemental application. The number of

manufacturing changes currently reported in supplements that will be reported in annual reports is approximately 1,283.

For example, under the previous regulations, all manufacturing site changes for drug products required prior approval. Now only a few types of drug product manufacturing site changes must be submitted in a prior approval supplement. The majority can be submitted in a changes-being-effected-in–30-days supplement or in an annual report. Moreover, FDA further reduced many reporting requirements from the levels recommended in previous FDA guidances. For example, the SUPAC guidances recommended notification in an annual report when moving production operations between buildings at the same manufacturing site. Now, generally no notification is required for such changes affecting drug products that were covered under the following SUPAC guidances: (1) "Immediate-Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation" (SUPAC–IR); (2) "Modified Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation" (SUPAC–MR); and (3) "Nonsterile Semisolid Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Release Testing, and In Vivo Bioequivalence" (SUPAC–SS).

FDA believes that the approach to postapproval changes embodied in the SUPAC guidances is consistent with section 506A of the act. However, certain aspects of these documents need to be updated to be consistent with specific requirements included in the act. For example, the new reporting category for

changes-being-effected-in-30-days supplements needs to be incorporated. FDA intends to update these guidances in the near future.

(Comment 2) Several comments said that FDA should adopt a "decision tree" or "key questions" approach in implementing section 506A of the act. The comments contend that this approach would allow a new approach to manufacturing changes that bases the regulatory reporting requirements on the results of scientific comparison of pre- and post-change material rather than allowing the reporting category to be determined by the potential for a change to have an adverse effect. The decision tree would focus on answering the key questions rather than exhaustive categorization of potential types of changes. One comment provided examples of decision trees for consideration.

FDA agrees that decision trees are a viable approach to postapproval manufacturing changes. However, a decision tree must consider the potential for a change to have an adverse effect to be consistent with section 506A of the act. The act bases the reporting category for a change on the potential for that change to have an adverse effect, not on the outcome of assessment studies. In some cases, based on the potential for an adverse effect, the act would require FDA to review a change prior to distribution of the drug product with the change, even if the applicant concludes that its studies and data demonstrate that the change has no significant adverse effect. FDA must evaluate whether the studies performed by the applicant were sufficient to assess the effect of the change and whether the data support the applicant's claim that the change has not adversely affected the identity, strength, quality, purity, and potency of the drug product as they may relate to the safety or effectiveness of a drug product. For example, an applicant may decide to develop an in vivo/in vitro correlation (IVIVC) for an extended release oral

dosage form (see CDER's guidance entitled "Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In vitro/In vivo Correlations" (September 1997)). If an IVIVC is established, the dissolution test will be used by the applicant as a surrogate for in vivo bioequivalence when it is necessary to document bioequivalence for postapproval changes. Establishing an IVIVC has a significant potential to affect the identity, strength, quality, purity, and potency of the drug product as they may relate to safety and effectiveness of the drug product, and requires a prior approval supplement. The applicant, based on its evaluation of the data, may believe that an IVIVC has been established but the agency, after evaluation of the applicant's data, may not concur. If the applicant decided that a prior approval supplement was not necessary based on its conclusions that an IVIVC has been established and implemented the change without waiting for the agency's concurrence, a drug product that is not bioequivalent could be distributed to the public.

FDA regulates a wide range of products, and a decision tree should address the fact that the potential for adverse effect will vary depending on factors such as the dosage form and route of administration. For example, in general, packaging changes that involve parenteral drug products are viewed by FDA to have a higher potential to have an adverse effect on the quality of the drug product as it relates to the safety and efficacy of the drug product than a packaging change for a solid oral dosage form product. Leachables from the packaging into parenteral drug products are more likely to occur than for a solid oral dosage form, and if leaching occurs, there is a higher potential for adverse reactions because of the route of administration. A safety determination by FDA must be made before the change is implemented. An

applicant wishing to rely on a decision tree can submit the decision tree using an appropriate mechanism, such as submission of a comparability protocol containing a decision tree, and FDA will evaluate the decision tree for consistency with section 506A of the act.

(Comment 3) Another comment said that the proposal consisted of heightened reporting requirements for changes in packaging materials for sterile liquid dosage forms.

Previously, under § 314.70(b), changes in packaging for sterile liquid dosage forms routinely required prior approval by FDA before they could be implemented. The final rule, at § 314.70(b)(2)(iii), still emphasizes the importance, from the safety perspective, of ensuring the sterility of drug products by requiring that changes that may affect drug product sterility assurance be reported in a prior approval supplement. However, the guidance "Changes to an Approved NDA or ANDA," announced elsewhere in this issue of the **Federal Register**, includes certain changes in the packaging of these products that can be implemented by means other than prior approval supplements. This action has reduced, rather than heightened, the regulatory burden relating to the packaging of sterile liquid dosage forms. FDA has included these changes in the guidance because, as stated in the proposal, the agency believes it can more readily respond to knowledge gained from manufacturing experience, further research and data collection, and advances in technology by issuing regulations that set out broad, general categories of manufacturing changes and by using guidance documents to provide FDA's current thinking on the specific changes that fall into those general categories (64 FR 34608 at 34610). Section 506A of the act explicitly provides FDA the authority to use guidance documents to determine the type of changes that

do or do not have a substantial potential to adversely affect the safety or effectiveness of the drug product. As discussed previously in this document, the use of guidance documents will allow FDA to more easily and quickly modify and update important information. Guidance documents will be developed according to the procedures set out in FDA's good guidance practices (see the **Federal Register** of September 19, 2000 (65 FR 56468), and 21 CFR 10.115).

(Comment 4) Another comment requested that FDA specifically address in the final rule and/or guidance or in separate guidance how a change in the device aspect of a drug-device combination product is to be reported in applications. The comment said that when establishing rules for reporting changes in packaging and packaging components, FDA should not simply apply the rules for changes to drugs and biologics to the device-like aspects of combination products. Rather, the comment said, FDA should consider how the equivalent change is managed for the analogous medical device and apply that approach.

CDER and CBER work cooperatively with the Center for Devices and Radiological Health (CDRH) in the review of drug-device combinations. Determinations as to which regulations apply to a given combination product are product and application specific. Sponsors of combination products should consult with the Center that provided the approval of their application and with the Office of Combination Products to determine what requirements are applicable to the changes they wish to make to their product.

(Comment 5) Several comments said that the proposal put an overwhelming emphasis on postapproval changes for drug products and little on drug substances. The comments identified the following concerns: (1) The

proposal is written entirely from the perspective of NDA and ANDA applicants and includes nothing for Drug Master File (DMF) holders; (2) a reporting classification system depending on the potential of a change to have an impact may usually work in the drug product area but is less apt to work for the drug substance, where the actual change may only be gauged by the data obtained when the change is made; and (3) the processes used in drug product and drug substance manufacturing differ greatly, making it difficult to determine how the changes outlined for drug products apply to drug substances. Several comments said that a separate document addressing changes relating to drug substances should be prepared.

The regulations emphasize changes in drug products and are written for NDA and ANDA applicants because the regulations describe the procedures for notifying FDA about changes in conditions established in an approved drug product application. Changes in a drug substance are only one of many types of changes that may occur in a drug product application. FDA has provided specific recommendations on drug substance changes in the guidance entitled "Changes to an Approved NDA or ANDA." In the **Federal Register** of February 16, 2001 (66 FR 10699), the agency announced a guidance that focuses specifically on postapproval manufacturing changes for certain drug substances entitled "BACPAC I: Intermediates in Drug Substance Synthesis, Bulk Actives Postapproval Changes: Chemistry, Manufacturing, and Controls Documentation" (the BACPAC I guidance). FDA believes that the BACPAC I guidance addresses the concerns expressed in the comments.

(Comment 6) Several comments reiterated comments previously provided to the agency on the guidances entitled "BACPAC I" and "Changes to an

Approved NDA or ANDA," and asked FDA to consider these comments in finalizing the proposed regulation.

FDA has considered and addressed these resubmitted comments in this document to the extent that they were applicable to the proposed regulation.

(Comment 7) Another comment said that FDA should provide for realistic and workable filing mechanisms and requirements with regard to changes in the manufacturing of drug substances where the information is included in DMFs.

The regulations and companion guidance entitled "Changes to an Approved NDA or ANDA" provide recommendations on reporting changes in the conditions established in an approved application, including changes in drug substance covered by DMFs. Issues relating to DMFs and how these are used in the application review process are outside the scope of this rulemaking.

(Comment 8) One comment stated that the rule should clearly address how changes in the manufacture of pharmaceutical packaging and pharmaceutical packaging components are to be handled. The comment said that the current regulation and the proposal and guidance address this issue incompletely, and frequently packaging and packaging component manufacturers are left to try to interpret the regulation as it applies to packaging.

FDA has clarified the requirements for packaging components in the final regulations as a result of the public comments and has included information on this topic in the guidance "Changes to an Approved NDA or ANDA."

(Comment 9) Several comments said that the use of broad and vague terms (e.g., any change, may impact) should be minimized. The comments said that such terms lend themselves to different interpretations, are likely to cause

confusion and inconsistent application, and are likely to result in more burdensome reporting requirements for changes that would be more appropriately categorized as moderate and/or minor changes. One comment said that FDA should revise these terms, and suggested adding the modifier "significant" or "significantly" in several instances to sharpen the intended meaning. The comment said that since the term "significant" is itself undefined, it suggests that, in this context, "significant" means "likely to adversely affect the identity, strength, quality, purity or potency of the related product."

FDA agrees that the use of broad and vague terms should be minimized and has clarified the regulation, as appropriate, in response to comments received on the use of such terms as "any change" and "may impact," and those comments suggesting adding the term "significant."

(Comment 10) One comment asked whether the final regulations will contain references to appropriate guidance documents.

The final regulations do not reference specific guidance documents. FDA continues to update and develop guidances to address particular regulatory and scientific issues, and any references included in a regulation may quickly become outdated. Guidances that provide FDA's current thinking on specific topics can be located on the Internet at *http://www.fda.gov/cder/guidance/index.htm* and *http://www.fda.gov/cber/guidelines.htm*.

(Comment 11) One comment said that although the proposal applies only to human drugs and biologics, the Center for Veterinary Medicine (CVM) may be preparing a similar proposal and may be compelled to apply most if not all of the principles described in the proposed rule. The comment said that the animal drug industry is very pleased with the successful 1996 CVM

initiative, "Alternate Administrative Process for the Implementation and Submission of Supplemental Chemistry, Manufacturing and Control Changes (AAP)." The comment said that its support of the Modernization Act was given based on the legal interpretation that the Modernization Act did not preclude the continuation of the AAP program. The comment said that the AAP program succinctly provides a process for determining minor supplemental chemistry, manufacturing, and control changes that are reported on a biennial basis. The comment continues to strongly support the concepts embodied in the AAP and is concerned that implementation of the proposed rule would be more burdensome, on both FDA and industry, than the AAP. The comment said that CVM and Animal Health Institute (AHI) member companies have had 3 years of successful implementation of this program and believe that the proposed rule, if applied to animal drugs, would be a major step backwards.

Comments relating to the AAP are outside the scope of this rulemaking and should be directed to the proposed rule for veterinary drug products entitled "Supplements and Other Changes to Approved New Animal Drug Applications" (published in the **Federal Register** of October 1, 1999 (64 FR 53281)) (the October 1999 proposal).

B. Definitions

FDA proposed to amend the definitions sections of the regulations on applications for FDA approval to market a new drug (§ 314.3 (21 CFR 314.3)) and a biological product (§ 600.3 (21 CFR 600.3)) by adding definitions for "specification" and "validate the effects of the change." Proposed §§ 314.3(b) and 600.3(hh) defined "specification" as the quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved application to confirm the quality of drug substances, drug products,

intermediates, raw materials, reagents, and other components including container closure systems, and in-process materials. The term "acceptance criteria" refers to numerical limits, ranges, or other criteria for the tests described.

FDA has revised the proposed definition of specification to make the use of the term "component" consistent with the definition of "component" at § 210.3 (21 CFR 210.3). FDA has revised the definition as follows:

Specification means the quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved application to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, components, in-process materials, container closure systems, and other materials used in the production of a drug substance or drug product. For the purpose of this definition, *acceptance criteria* means numerical limits, ranges, or other criteria for the tests described.

FDA has made the same changes to proposed § 600.3(hh) (new § 600.3(jj)) and clarified the definition of specification for biological products by replacing the phrase "drug substances, drug products" with "products." The term "products" is defined in § 600.3(g).

(Comment 12) Several comments stated that "intermediates, raw materials, reagents, and other components including container closure systems, and in-process materials" should be deleted from the definition of specification, and changes for these materials should be handled separately from the final rule and final guidance. The comments said that the definition is not consistent with the International Conference on Harmonisation (ICH) guidance on specifications entitled "Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances" (ICH Q6A), which includes only drug substance and drug product. The comments said that to

include items beyond the drug substance and drug product represents a level of complexity that would be better dealt with in guidances that can adequately evaluate the significance of changes to specific items.

FDA declines to revise the definition as requested. Section 505 of the act (21 U.S.C. 355) requires that a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of a drug be provided in an application. The regulations at § 314.50(d)(1) (21 CFR 314.50(d)(1)) require that an application include specifications as are necessary to ensure the identity, strength, quality, purity, and potency of the drug substance and drug product. Moreover, the regulation at § 314.50(d)(1)(ii)(a) specifically requires that specifications be provided for each component. It identifies specifications for container closures systems as an example of a specification needed to ensure the identity, strength, quality, purity, and potency of the drug product. For biologics, an applicant must submit a full description of manufacturing methods (§ 601.2 (21 CFR 601.2)). Intermediates, raw materials, reagents, container closure systems, in-process materials and other materials that are used in the manufacture of drug substances, drug products, and biologics are considered part of the manufacturing method and can have a direct effect on the identity, strength, quality, purity, and potency of the drug substance, drug product, or biologic. While the extent of a specification (e.g., number or type of tests, strictness of acceptance criteria) for these materials may vary depending on their use in a given manufacturing process, FDA has required specifications for these materials to be included in applications as part of the description of the manufacturing method and will continue to do so.

The ICH Q6A guidance and the ICH guidance on specifications entitled "Test Procedures and Acceptance Criteria for Biotechnology/Biological Products" (ICH Q6B) are limited in scope. For example, ICH Q6A specifically excludes fermentation products. Interpreting the limitations of the ICH guidances to mean that specifications are not required for fermentation products or other materials outside the scope of ICH Q6A or ICH Q6B would be incorrect.

FDA requires specifications for intermediates, raw materials, reagents, container closure systems, in-process materials, and other materials used in the manufacturing process to be included in the application and, therefore, has included these materials in the definition of specification. Any changes in a specification, except editorial, must be reported to FDA and applicants need guidance on how to implement these changes. FDA declines deferring recommendations on these changes to a later guidance and has provided guidance on the recommended reporting categories for changes in specifications in FDA's guidances entitled "Changes to an Approved NDA or ANDA" and "Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products" (July 1997).

(Comment 13) One comment said that the term "specifications and test procedures" was used in part 314 (21 CFR part 314) in the past, but the proposal replaced this with the term "specification," which is intended to mean both tests and specifications. The comment said that using one word to represent several things is confusing and recommended retaining the previous terminology.

FDA declines to revise the use of the term "specification" as requested. In the past, "specification" as used in part 314 meant numerical limits, ranges,

or other criteria for a test. In developing the ICH Q6A and ICH Q6B guidances, FDA agreed to define specification differently. A specification, as defined in ICH Q6A and ICH Q6B, includes tests, analytical procedures, and acceptance criteria. FDA has used the ICH Q6A and ICH Q6B terminology in this rule to promote consistency with the ICH documents.

(Comment 14) One comment identified various types of specification changes and recommended how these should be categorized and reported.

FDA declines to expand the discussion of specification changes in the regulation. As stated in the June 1999 proposal, the agency believes it can more readily respond to knowledge gained from manufacturing experience, further research and data collection, and advances in technology by issuing regulations that set out broad, general categories of manufacturing changes and by using guidance documents to provide FDA's current thinking on the specific changes that fall into those general categories (64 FR 34608 at 34610). FDA has provided recommendations on specific changes in specifications in FDA's guidances entitled "Changes to an Approved NDA or ANDA" and "Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products."

Proposed §§ 314.3(b) and 600.3(ii) defined "validate the effects of the change" as an assessment of the effect of a manufacturing change on the identity, strength, quality, purity, or potency of a drug as these factors relate to the safety or effectiveness of the drug.

(Comment 15) Many comments recommended that FDA replace the terms validate or validation with assess or assessment. Several comments stated that although FDA used the terms consistently with Congress's use of the terms in section 506A of the act, they believe that the term "validate" is likely to

cause confusion because this term has long been associated with and has specific meaning under FDA's CGMP regulation.

FDA agrees and has revised the definition as requested by replacing "validate" with "assess." In addition, as a result of comments requesting that the use of the terms drug, drug product, drug substance, and product be standardized, FDA has clarified the definition in § 314.3(b) by replacing the term "drug" with "drug product." FDA has clarified the definition in proposed § 600.3(ii) (new § 600.3(kk)) by replacing the term "drug" with "product." The terms drug product and products are defined at §§ 314.3(b) and 600.3(g), respectively. FDA, on its own initiative, has also revised the phrase "purity, or potency" to "purity, and potency" and the phrase "as these factors relate" to "as these factors may relate" to be consistent with section 506A(b) of the act, and the phrase "to assess the effect" to "to evaluate the effects" for clarity. FDA notes that while the effect of a manufacturing change on the identity, strength, quality, purity and potency of a drug or biological product is to be assessed, this assessment could involve testing of materials directly affected by a change (e.g., drug substance) in addition to or instead of drug or biological product testing.

(Comment 16) Several comments recommended that unambiguous definitions of substantial, moderate, and minimal potential for adverse effects be added to the regulation, and one comment recommended that examples be added for clarification. One comment asked that a definition of natural product be added.

FDA declines to revise the regulation as requested. The regulations apply to many types of changes for a broad spectrum of products. The meaning of substantial, moderate, and minimal potential for adverse effects is most easily

illustrated through the use of examples. FDA has decided to use guidance documents to provide specific examples of changes that are considered to have substantial, moderate, and minimal potential to have adverse effect rather than enumerate them in the regulation. FDA has provided many examples of types of changes in FDA's guidances entitled "Changes to an Approved NDA or ANDA" and "Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products." In addition, FDA has provided an explanation of the term "natural products" in the guidance on "Changes to an Approved NDA or ANDA."

(Comment 17) Concerning the regulations on the content and format of an application in § 314.50, one comment noted that § 314.50(d)(1)(i) and (d)(i)(ii) includes the following statement for drug substance and drug product: "Reference to the current edition of the USP/NF [National Formulary] may satisfy the relevant requirements in the paragraph." The comment said it appeared that this statement was being deleted and contended that it should be retained in the regulations.

FDA is clarifying that this sentence has not been deleted from § 314.50(d)(1)(i) or (d)(1)(ii). As stated in the June 1999 propoal, FDA is revising the first two sentences of these paragraphs.

C. Changes to an Approved Application

Proposed § 314.70(a)(1) set forth general requirements under which an applicant must notify FDA about each change in each condition established in an approved application beyond the variations already provided for in the application. The notice is required to describe the change fully. Depending on the type of change, the applicant must notify FDA about the change in a

supplement under § 314.70(b) or (c) or by inclusion of the information in an annual report under § 314.70(d).

(Comment 18) One comment said that the statements "an applicant must notify FDA about each change in each condition established in an approved application beyond the variations already provided for in the application" and that "the notice is required to describe the change fully" should be clarified because it could be overly burdensome from the standpoint that some changes, for example, changes made to batch records submitted as part of the application, may not require reporting under § 314.70.

FDA declines to revise the regulation as requested and notes that the agency does not expect to be informed about nonsubstantive editorial changes in information included in an application. Nonsubstantive editorial changes include such changes as corrections of spelling or typographical errors or reformatting of documents (e.g., batch records, specification sheets).

Proposed §§ 314.70(a)(2) and 601.12(a)(2) (21 CFR 601.12(a)(2)) required the holder of an approved application to assess the effects of manufacturing changes on the identity, strength, quality, purity, or potency of a drug as these factors may relate to the safety or effectiveness of the drug before distributing a drug made with a manufacturing change.

(Comment 19) A few comments said that the proposal would increase the reporting burden despite the specific provision in the Modernization Act for having assessment data at the time of submission of manufacturing change supplements. The comment said that the Modernization Act specifies that a drug made with a manufacturing change may be distributed only after completing studies that assess the effects of the change. The comment said that the legislative intent of the Modernization Act is that if appropriate studies

comparing pre- and postchange material are performed and no evidence of an adverse effect is found, then a reduced reporting category for the evaluated changes is appropriate. The comment reasoned that a given proposed manufacturing change can indeed have substantial potential for adverse effects at its inception because little might be known about the impacts of the change. However, by the time actual material has been made with the change and assessment studies have been successfully completed, most or all of the potential impacts of the change have been eliminated. The comment said that the assessment information should permit a reduced reporting requirement.

FDA disagrees with these comments. Section 506A(c)(2) of the act states that a major manufacturing change is "a change that is determined by the Secretary to have substantial *potential* to adversely affect the identity, strength, quality, purity, or potency of the drug as they may relate to the safety or effectiveness of a drug" (emphasis added). The act bases the reporting category for a change on the potential for that change to have an adverse effect, not on the outcome of the assessment studies. The comment implies that the only changes that would be reported in a prior approval supplement are those where the applicant's studies to assess the effects of the change demonstrate that there is in fact an adverse effect on the identity, strength, quality, purity, or potency of the drug as they may relate to the safety or effectiveness of a drug product. FDA does not believe that this was the intent of Congress. Some manufacturing changes have an adverse effect on the identity, strength, quality, purity, or potency of the drug product. In many cases, the applicant chooses not to implement these manufacturing changes, but sometimes the applicant wishes to do so. If an assessment indicates that a change has adversely affected the identity, strength, quality, purity, or potency of the drug product, the change

must be submitted in a prior approval supplement, regardless of the recommended reporting category for the change. For example, a process change recommended for a changes-being-effected-in-30-days supplement could cause the formation of a new degradant that requires qualification and/or identification. The applicant may believe that there are no safety concerns relating to the new degradant. Even so, the applicant must submit this change in a prior approval supplement with appropriate information to support the continued safety and effectiveness of the product. During the review of the prior approval supplement, FDA will assess the impact of any adverse effect on the drug product as this change may relate to the safety or effectiveness of the drug product.

FDA also received comments requesting that the term "assess" be used instead of "validate." FDA has made this change in §§ 314.70(a)(2) and 601.12(a)(2), where appropriate. In § 314.70(a)(2), FDA, on its own initiative, has deleted the phrase "on the identity, strength, quality, purity, and potency of the drug product as these factors may relate to the safety or effectiveness of the drug product" because "assess the effects of the change," as defined in § 314.3(b), includes this phrase.

Proposed §§ 314.70(a)(3) and 601.12(a)(3) stated that notwithstanding the supplement submission requirements, an applicant must make a manufacturing change in accordance with a regulation or guidance that provides for a less burdensome notification of the change.

(Comment 20) Several comments noted that they were pleased that the provision that a change can be made "in accordance with a regulation or guidance that provides for a less burdensome notification of the change" was

proposed because it permits less burdensome reporting mechanisms for changes.

FDA acknowledges these comments and has retained this provision in the final rule.

Proposed §§ 314.70(a)(4) and 601.12(a)(4) stated that the applicant must promptly revise all promotional labeling and advertising to make it consistent with any labeling change implemented in accordance with this section.

(Comment 21) Several comments said that the previous provisions in § 314.70 limited the requirement to promptly revise all promotional labeling and advertising to those changes that were to be filed in a changes-being-effected supplement, and that this requirement is not necessary for the type of labeling changes that would be filed in an annual report. The comments suggested that this requirement be limited to those labeling changes that would be filed in supplemental applications.

The agency agrees with the comments and has revised § 314.70(a)(4) to require applicants to revise promotional labeling and advertising to make it consistent with labeling changes implemented in accordance with § 314.70(b) and (c). In addition, § 601.12(a)(4) requires applicants to revise promotional labeling and advertising to make it consistent with labeling changes implemented in accordance with § 601.12(f)(1) and (f)(2).

Proposed § 314.70(a)(5) stated that, except for a supplement providing for a change in the labeling, the applicant must include in each supplemental application providing for a change under paragraph (b) or (c) a statement certifying that a field copy of the supplement has been provided to the applicant's home FDA district office.

(Comment 22) A few comments requested that FDA clarify whether the field copy that is to be sent to the applicant's "home FDA district office" should be the FDA office where the change is being made or the FDA office in the district of the company's corporate headquarters from where the submission documents are sent. The comments also said that if the field copy should be sent to the office where the change is being made, FDA should clarify what FDA office(s) serve for changes made internationally. The comment said that the clarification will help to ensure that the appropriate documents get to the correct FDA district office.

Mailing information for field copies is provided in § 314.440(a)(4). Currently, FDA recommends that the "applicant's home FDA district office" referred to in § 314.440(a)(4) be the district office where the applicant's headquarters is located. FDA has clarified this provision by cross-referencing § 314.440(a)(4). Section 314.440(a)(4) also provides mailing information for international applicants. FDA, on its own initiative, has also clarified the provision by adding "amendments to supplements." A field copy of an amendment to a supplement, which is submitted by an applicant to incorporate additional or corrected information into their original supplement, is currently required under § 314.440(a)(4).

Proposed §§ 314.70(a)(6) and 601.12(a)(5) added a requirement that a list of all changes contained in the supplement or annual report must be included in the cover letter for the supplement or annual report.

(Comment 23) Many comments agreed that a list of changes should be included in the cover letter for a supplement. However, the comments disagreed that a list of all changes contained in the annual report should be included in a cover letter. The comments said that including a list in a cover

letter to an annual report is overburdensome because cover letters are not required for annual reports, only a Form FDA 2252, and a list of changes is already provided in a section of an annual report. Several comments said that an applicant should have the option of providing the list in a location other than the cover letter, such as at the beginning of the supplement.

FDA agrees with the requests to permit the list of changes to be provided in the summary section of the annual report and has revised §§ 314.70(a)(6) and 601.12(a)(5) to require changes to be listed in the cover letter only for supplemental applications.

An annual report is required to contain a brief summary of significant new information from the previous year that might affect the safety, effectiveness, or labeling of the drug product (§ 314.81(b)(2)(i)). FDA's guidance for industry entitled "Format and Content for the CMC Section of an Annual Report" (September 1994) states, regarding the summary of new information, that the firm should include in the annual report "a brief summary of all changes made to the application during the reporting period including changes made in accordance with approved supplements under 21 CFR 314.70(b) and * * * supplements under 21 CFR 314.70(c)* * *." Supplements are not required to have a summary section (§ 314.50(c)).

FDA is requiring that a list of changes be provided in both supplemental applications and annual reports. FDA proposed this requirement as a means to more efficiently locate and identify changes in what are often documents of substantial length. The list will also allow FDA to quickly assess whether the appropriate reporting category was used. To achieve these objectives, it is essential that the list be in a consistent location for each type of submission.

(Comment 24) Several comments were concerned that the list of changes, if included in a cover letter, would not be considered confidential information.

The standards for disclosing specific information from a cover letter or application do not differ depending on where this information is provided. Information that is exempted from disclosure (e.g., trade secret or confidential commercial information) is not disclosed whether it is in a cover letter or an application (see also §§ 314.430 and 601.51 (21 CFR 601.51)).

(Comment 25) One comment requested that the phrase "list of all changes" be revised to "a brief summary of major changes."

FDA declines to revise the regulation as suggested. Each change, including moderate and minor changes, should be listed. FDA notes that the description of the listed change should be in sufficient detail to allow the agency to quickly determine whether the appropriate reporting category for the change has been used. For example, describing a change as "a change in the drug product specification" does not provide sufficient detail. A description such as "deletion of the friability test and associated acceptance criteria and analytical procedure from the drug product specification" would allow FDA to quickly assess whether the appropriate reporting category was used. The detailed information about each change and the information developed to assess the effects of the change would be provided in the supplement or elsewhere in the annual report.

(Comment 26) Several comments suggested changes in Form FDA 2252 that accompanies an annual report.

FDA declines to revise Form FDA 2252 because it is not within the scope of this regulation.

D. Changes Requiring Supplement Submission and Approval Prior to Distribution of the Product Made Using the Change (Major Changes)

Proposed § 314.70(b)(1) required that a supplement requiring prior approval must be submitted for any change in the product, production process, quality controls, equipment, or facilities that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product.

(Comment 27) Many comments asked whether a prior approval supplement would be required even if the applicant has demonstrated that the change has no significant adverse affect.

Section 506A(c)(2) of the act states that a major manufacturing change is "a change that is determined by the Secretary to have substantial potential to adversely affect the identity, strength, quality, purity, or potency of the drug as they may relate to the safety or effectiveness of a drug." The act bases the reporting category for a change on the potential for that change to have an adverse effect, not on the outcome of the assessment studies. FDA would expect a prior approval supplement to be submitted for a change that has substantial potential to adversely affect the identity, strength, quality, purity, or potency of a drug product even if the applicant concludes that their studies and data demonstrate that the change has no adverse effect. Prior to distribution of the drug product made with the change, FDA must evaluate whether the studies performed by the applicant were sufficient to assess the effect of the change and that the data support the applicant's claim that the change has not adversely affected the identity, strength, quality, purity, or potency of the drug product as they may relate to the safety or effectiveness of a drug product.

(Comment 28) One comment said that section 506A of the act identifies major changes as formulation, specification, or those requiring studies in accordance with part 320 (21 CFR part 320) to demonstrate the equivalence of the drug product to the drug product as manufactured without the change or to the reference listed drug. The comment said that FDA has proposed prior approval supplements for changes that are clearly outside of these three major change categories. Another comment said it appears that FDA has overutilized section 506A(c)(2)(C) of the act.

FDA disagrees that it has overutilized this part of the act. In addition to the three major changes identified previously in this document, section 506A(c)(2)(C) of the act states that a major change "is another type of change determined by the Secretary by regulation or guidance to have a substantial potential to adversely affect the safety or effectiveness of the drug." In previous regulations, many manufacturing changes required prior approval supplements. FDA has used this provision of the act to identify a limited number of changes that it considers to have a substantial potential to adversely affect the identity, strength, quality, purity, or potency of the drug as they may relate to the safety or effectiveness of a drug. The regulation reduces the overall number of supplements requiring FDA approval prior to product distribution. In addition, many changes that are currently reported in supplements will be able to be reported in annual reports. The regulation will not increase the number of annual reports but will allow applicants to include in an annual report information currently required to be reported to the agency in a supplemental application. Moreover, FDA further reduced many reporting requirements from the levels recommended in previous FDA guidances.

Proposed § 314.70(b)(2)(i) provided that, except as provided in § 314.70(c) and (d), prior approval is required for changes in the qualitative or quantitative formulation of the drug, including inactive ingredients, or in the specifications provided in the approved application.

(Comment 29) A few comments recommended that proposed § 314.70(b)(2)(i) be revised to better reflect section 506A(c)(2)(A) of the act which allows exceptions to the requirement to obtain prior approval before changing the qualitative or quantitative formulation of the drug. One comment recommended the provision be revised to state: "Except as provided in paragraphs (c) and (d) of this section or exempted by regulation or guidance * * *."

FDA declines to revise the regulation as requested. Section 506A(c)(2)(A) of the act states that a prior approval supplement is required when a change "is made in the qualitative or quantitative formulation of the drug involved or the specifications in the approved application or license * * * (unless exempted by the Secretary by regulation or guidance * * *)." Proposed § 314.70 is consistent with the provisions of the act. Exemptions by regulation are provided in § 314.70(c) or (d). This language is already included in § 314.70(b)(2)(i). In addition, FDA may use guidance documents to provide for a less burdensome notification of a specific change. This exemption is included in § 314.70(a)(3) and applies to § 314.70(b)(2)(i) as well as the other changes listed in § 314.70.

(Comment 30) Several comments noted that the SUPAC guidances allowed for some changes in qualitative or quantitative formulation of the drug product to be filed in changes-being-effected supplements or annual reports. One

comment said that the regulations should follow the standards in the SUPAC guidances.

FDA has not incorporated the qualitative and quantitative formulation change information from the SUPAC guidances in the regulation because, as stated in the proposal, the agency's approach is to issue regulations that set out broad, general categories of manufacturing changes and use guidance documents to provide FDA's current thinking on the specific changes included in those categories.

(Comment 31) Several comments said that changes in specification to comply with an official compendium should not require prior approval supplements.

FDA is not requiring prior approval supplements for specification changes made to comply with an official compendium. A complete discussion of this issue is provided under section III.F of this document, "Changes To Be Described in the Next Annual Report," in response to comments on § 314.70(d)(2)(i).

(Comment 32) One comment recommended the proposed language be revised to limit specification changes to those for drug substance or drug product.

FDA considers a specification to be a quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved application to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, components, in-process materials, container closure systems, or other materials used in the production of a drug substance or drug product. Therefore, FDA declines to revise the proposal as suggested.

Proposed § 314.70(b)(2)(ii) required prior approval for changes requiring completion of studies in accordance with part 320 to demonstrate the equivalence of the drug to the drug as manufactured without the change or to the reference listed drug.

(Comment 33) One comment said that reference to part 320 suggests that bioequivalence must be addressed for "a change in the manufacturing process * * *." The comment said that this will lead to significant interpretation issues. The comment said that a selective subset of major manufacturing changes that truly have "substantial potential" should be specified here. Another comment said that when the product is a true solution, changes to the manufacturing process (not formulation) are highly unlikely to change the formulation and additional clinical (bioequivalence) studies should not always be required.

FDA declines to revise the proposal based on these comments. The requirements for when a study is needed to demonstrate the equivalence of a drug product made with the proposed change to a drug product made without the change or to the reference listed drug are provided in part 320. Part 314 is not intended to supplement, supersede, or clarify these requirements. Section 314.70(b)(2)(ii) specifies only that if such a study is required under part 320 to support a postapproval change, the postapproval change must be submitted using a prior approval supplement. Changes that require a study under part 320 are considered major changes that have a significant potential to affect the identity, strength, quality, purity, or potency of the product as it relates to the safety or effectiveness of a product, and FDA would need to review such studies before a product made with the change is placed into distribution.

Proposed § 314.70(b)(2)(iii) required prior approval for changes that may affect product sterility assurance, such as changes in product or component sterilization method(s) or an addition, deletion, or substitution of steps in an aseptic processing operation.

(Comment 34) Many comments stated that the proposed language was too broad and should be modified to state "changes that may significantly affect product sterility assurance" or "changes that significantly affect product sterility assurance". One comment said that the term "may affect" is not appropriate because any change may affect one or more attributes of a sterile drug.

Sterility of drug products or drug substances is a fundamental and essential quality attribute of these drugs and is a critical aspect of the safety assessment. The manufacture of a sterile drug is an exacting, difficult, and highly controlled series of processes, especially in the case of aseptically processed drugs. The concept of significance or "significantly affect" implies that a measurement of an attribute, such as sterility, can be made. However, no test is sensitive enough to detect unacceptable sterility assurance levels (i.e., the probability of a nonsterile unit). For example, a batch of drug product tested using the standard drug product sterility test described in the USP/NF will fail the sterility test only when at least 14 percent of the batch is contaminated (95 percent confidence level). This sterility assurance level is unacceptable. The probability of nonsterile units for terminally sterilized and aseptically processed drugs is normally expected by FDA to be less than 0.0001 percent and 0.1 percent, respectively. FDA ensures the safety of sterile drugs by assessing the efficacy of a given sterilization process for a specific drug and by ensuring that the facilities producing sterile drugs comply with CGMPs. The

assessment of the efficacy of a sterilization process includes review of multiple protocols and scientific experiments designed to demonstrate that the sterilization process and associated control procedures can reproducibly deliver a sterile product. The data derived from the experiments and control procedures allow certain conclusions to be drawn about the probability of nonsterile units. A properly validated sterilization process will provide the sterility assurance level required by FDA to ensure the safety of sterile drugs. Because of the lack of adequate test procedures for assessing sterility and the complexity in evaluating the process validation and controls information to determine the level of sterility assurance that a given process provides for a specific drug, FDA has used the term "may affect" and declines to revise the proposal as suggested.

(Comment 35) Many comments stated that the proposed language should be clarified to state "changes that may adversely affect product sterility assurance * * *" or "changes that may reduce (or decrease) product sterility assurance * * *".

New § 314.70(b)(1) already identifies that the changes that should be submitted in prior approval supplements are those that have a substantial potential to have an "adverse effect." FDA declines to revise proposed § 314.70(b)(2)(iii) as requested because the addition of the term "adversely" is redundant. FDA emphasizes that the assessment of whether a change may adversely affect sterility assurance is a complex and multidimensional analysis. For example, a change to a more stringent terminal sterilization process, while in theory providing a lower probability of nonsterile units, may damage the container closure system so that sterility of individual units could not be maintained.

(Comment 36) Several comments said that the proposed language is too restrictive because it indicates that all changes to sterile products should be submitted in prior approval supplements. The comments said that this contradicts what is in the guidance entitled "Changes to an Approved NDA or ANDA," which identifies some changes that do not have to be filed in prior approval supplements. One comment identified specific examples of manufacturing changes for sterile products and said that these should not be considered major changes.

FDA considers changes that may affect the sterility assurance level of a drug to have significant potential to affect the safety of the drug. Therefore, FDA has identified this change as one that requires prior approval. As stated in the June 1999 proposal, this rulemaking sets out broad, general categories of manufacturing changes, and the agency uses guidance documents to provide FDA's current thinking on the specific changes included in those categories. Under § 314.70(a)(3), an applicant must notify FDA of a manufacturing change in accordance with either a regulation or a guidance that addresses the same issues as the regulation but that provides for a less burdensome notification of the change than the regulation (for example, by submission of a supplement that does not require approval prior to distribution of the product). For example, in the guidance entitled "Changes to an Approved NDA or ANDA," FDA has identified less burdensome reporting categories for certain changes that it believes have less potential to affect sterility assurance and consequently the safety of the drug.

(Comment 37) A few comments said that this provision increases the regulatory burden with respect to sterile products. The comments said that only fundamental changes to sterile processing require prior approval.

FDA disagrees with this comment. Under the previous regulations at § 314.70, manufacturing site, processing, and packaging changes for sterile drugs almost always required a prior approval supplement (previous § 314.70(b)(1)(iv), (b)(1)(v), (b)(2)(iv), (b)(2)(v), and (b)(2)(vi)). Under § 314.70(c) and (d), certain changes related to sterile drugs may be submitted in changes-being-effected supplements or annual reports (for example, § 314.70(d)(2)(i) and (iii)). In the guidance entitled "Changes to an Approved NDA or ANDA," FDA has identified many changes related to sterile drugs that may now be submitted in changes-being-effected supplements or annual reports.

Proposed § 314.70(b)(2)(iv) required prior approval for changes in the synthesis or manufacture of the drug substance that may affect the impurity profile and/or the physical, chemical, or biological properties of the drug substance.

(Comment 38) One comment said that the proposal should be revised to state "Changes in the route of synthesis or * * *." Changes such as an additional recrystallization step (using the same solvents, and so forth) should be considered for changes-being-effected status.

FDA declines to revise the proposal as suggested. Changes in the synthesis, including the route of synthesis, may have an effect on the impurity profile and/or the physical, chemical, or biological properties of the drug substance. For example, a change in a solvent used in the crystallization step may affect the impurity profile and physical properties of the drug substance even though this change would not be considered a change in the "route of synthesis."

(Comment 39) Several comments stated that the proposed language should be clarified to state "changes that may adversely affect the impurity profile

* * *'' because changes that improve the quality of the drug substance should not require a prior approval supplement.

New § 314.70(b)(1) states that the changes that should be submitted in prior approval supplements are those that have a substantial potential to have an ''adverse effect.'' FDA declines to revise the provision as requested because the addition of the term ''adversely'' is redundant.

(Comment 40) One comment suggested that FDA change ''may affect the impurity profile of the drug product'' to ''are likely to affect the impurity profile of the drug product.'' The comment said that many factors could affect the impurity profile, and this stringent reporting requirement should be reserved for factors that are likely to produce a change.

FDA believes the phrase ''may affect'' is appropriate because the decision on whether a change should be considered a major, moderate, or minor change is based on the potential for the change to adversely affect the identity, strength, quality, purity, or potency of the drug as they may relate to the safety or effectiveness of a drug product. FDA considers a change that ''may affect the impurity profile and/or the physical, chemical, or biological properties of the drug substance'' to be a change that has a substantial potential to result in an adverse effect and declines to delete ''may.''

(Comment 41) One comment said that inserting the clause ''beyond those studied in the pre-clinical studies and requiring a change in the approved specifications'' after impurity profile would add clarity. The comment said that according to the ICH guidance entitled ''Impurities in New Drug Substances'' (ICH Q3A), impurities below a certain threshold would not necessarily require registration.

The process of qualifying impurities and determining if a postchange impurity profile for a drug substance is equivalent or better than the impurity profile of the prechange material is a complex issue. FDA does not believe it is possible to clarify the regulations to adequately address the many different types of human drugs it regulates. For example, not all drug approvals require preclinical studies. FDA declines to revise the proposal as suggested. FDA published the BACPAC I guidance to provide recommendations on how to evaluate changes in impurity profiles.

(Comment 42) Several comments said that the proposed regulations were not consistent with the BACPAC I guidance. Several comments said that the proposal was much more restrictive than what was included in the BACPAC I guidance. One comment said that changes in drug substance synthesis route, which occur prior to the formation of key intermediates, should not be regarded as major changes, since the potential to impact the quality, strength, identity, and purity of the final product is low.

FDA declines to revise the regulations as requested. The BACPAC I guidance is an example of a guidance that permits certain specific changes that fall under the general category of a change that "may affect the impurity profile and/or the physical, chemical, or biological properties of the drug substance" to be reported using a less burdensome method of notification. Under § 314.70(a)(3), an applicant must notify FDA of a manufacturing change in accordance with either a regulation or a guidance that addresses the same issues as the regulation but that provides for a less burdensome notification of the change than the regulation (for example, by submission of a supplement that does not require approval prior to distribution of the product).

Proposed § 314.70(b)(2)(v) required prior approval for changes in labeling, except those described in § 314.70(c)(6)(iii), (d)(2)(ix), or (d)(2)(x).

On its own initiative, FDA has revised § 314.70(b)(2)(v) to add: "If applicable, any change to a Medication Guide required under part 208 of this chapter, except for changes in the information specified in § 208.20(b)(8)(iii) and (b)(8)(iv) of this chapter." This provision, which was previously in § 314.70(b)(3)(ii), was inadvertently omitted from the proposed rule.

(Comment 43) Many comments said that FDA should clarify "labeling" to indicate "drug product labeling" because drug substance labeling changes need not be submitted.

FDA declines to revise the regulations as requested. The term "labeling" in § 314.70 is consistent with "labeling" as used in part 201 (21 CFR part 201). Part 201 applies to the labeling of drugs and/or drug products.

Proposed § 314.70(b)(2)(vi) required prior approval for changes in a container closure system that controls drug delivery or that may affect the impurity profile of the drug product.

(Comment 44) Several comments requested that the proposed language be clarified to state "changes that may adversely affect the impurity profile * * *" or "changes that adversely affect the impurity profile ***."

FDA declines to revise the provision because the addition of the term "adversely" is redundant. New § 314.70(b)(1) already states that the changes that should be filed in prior approval supplements are those that have a substantial potential to have an "adverse effect." FDA believes the phrase "may affect" is appropriate because the decision on whether a change should be considered a major, moderate, or minor change is based on the potential for the change to adversely affect the identity, strength, quality, purity, or potency

of the drug as they may relate to the safety or effectiveness of a drug product. FDA considers a change that "may affect the impurity profile of the drug product" to be a change that has a substantial potential to result in an adverse effect and declines to delete "may."

(Comment 45) One comment requested clarification of what is meant by "controls drug delivery," such as quantity dispensed, machine calibration, and volume of fill.

For some drug products, the container closure system itself, rather than a person, regulates the amount of drug product that is administered to a patient. These container closure systems are considered to "control drug delivery." For example, a patient that uses a metered dose inhalation product as instructed cannot control the amount of drug product the container closure system delivers or verify that the appropriate amount has been administered. Where a drug product container closure system controls drug delivery, FDA requires information to be submitted to support that the container closure system can accurately and repeatedly deliver the required amount of drug product. The design and operation of these container closure systems is critical to ensure that the patient receives the correct dose. A drug product may not be safe or effective if a patient receives too much or too little of the drug product. Changes in these systems are considered to have a substantial potential to adversely affect the identity, strength, quality, purity, or potency of the drug as they may relate to the safety or effectiveness of a drug product. Container closure systems for drug products where a person controls the amount of drug product administered and/or which allow for verification that the appropriate amount has been administered (e.g., number of tablets,

milliliters of liquid) are not considered container closure systems that "control drug delivery."

(Comment 46) Another comment asked whether this section specifically refers to the final packaged product only.

Changes in "a container closure system that controls drug delivery" applies only to the marketed drug product container closure system, and the language has been revised in the final rule to clarify this. Changes that "may affect the impurity profile of the drug product" applies to any type of container closure system.

(Comment 47) One comment noted an apparent conflict between § 314.70(b)(2)(vi), which says that a "change in a container closure system that * * * may affect the impurity profile of the drug product" should be submitted in a prior approval supplement and § 314.70(c)(2)(i), which says that "a change in the container closure system that does not affect the quality of the final drug product" should be submitted in a changes-being-effected-in-30-days supplement. The comment said that this would allow for inconsistent and overly conservative interpretations of what might fall into this latter category.

FDA agrees that clarification of the wording in these two provisions of the regulations is needed. FDA has particular concerns about changes in the type (e.g., glass to high density polyethylene (HDPE), HDPE to polyvinyl chloride, vial to syringe) or composition (e.g., one HDPE resin to another HDPE resin) of packaging components because these changes may affect the impurity profile of the drug product. These concerns are compounded by the fact that, in most cases, the packaging component manufacturer considers the manufacturing process confidential information and discloses it only to FDA. Therefore, an applicant does not have knowledge of all potential impurities

that a different type or composition of a packaging component may introduce into a product. Depending on the dosage form affected and its route of administration, FDA may have to evaluate the safety of changes in the type or composition of a packaging component. Because of the safety concerns relating to new impurities from a packaging component with this type of change, FDA considers such changes to have a substantial potential to adversely affect the identity, strength, quality, purity, or potency of the drug as they may relate to the safety or effectiveness of a drug product. FDA has revised § 314.70(b)(2)(vi) to limit the requirement to situations involving changes in the type or composition of a packaging component. FDA considers a deletion or addition of a packaging component to fall within the meaning of a change in the type of packaging component. FDA may, through regulations or guidance, identify certain dosage forms and/or routes of administration where there is a lower potential for adverse effect and allow changes in type or composition of a packaging component in these situations to be reported in changes-being-effected supplements or annual reports.

For consistency with the proposal, FDA has revised § 314.50(d)(1)(ii)(*a*) to change "containers and closure systems" to "container closure systems."

Proposed § 314.70(b)(2)(vii) required prior approval for changes solely affecting a natural product, a recombinant DNA-derived protein/polypeptide product, or a complex or conjugate of a drug with a monoclonal antibody for the following:

(1) Changes in the virus or adventitious agent removal or inactivation method(s); (2) changes in the source material or cell line; and (3) establishment of a new master cell bank or seed.

(Comment 48) Several comments requested that FDA delete the reference to "natural products," while others requested that FDA provide a definition for natural products. A few comments asked whether fermentation-based products are considered natural products.

FDA declines to delete natural products from this provision. The changes identified in this provision are considered to be major changes and apply equally to a natural product, a recombinant DNA-derived protein/polypeptide, or a complex or conjugate of a drug substance with a monoclonal antibody. FDA has provided a definition of natural product in the guidance entitled "Changes to an Approved NDA or ANDA" but declines to provide the definition in the regulation because advancements in technology may require that the definition be revised. FDA has defined natural product in the guidance to mean "materials (e.g., drug substance, excipients) that are derived from plants, animals, or microorganisms. The specific recommendations for natural products are not applicable to inorganic compounds (e.g., salts, minerals)." Fermentation based products are considered natural products.

(Comment 49) A few comments said that this provision increases the regulatory burden with respect to natural products. One comment said that there was no need to distinguish a natural product, a recombinant DNA-derived protein/polypeptide, or a complex or conjugate of a drug substance with a monoclonal antibody from other products.

FDA disagrees with these comments. Under the previous regulations at § 314.70, many manufacturing process changes for drug substances and drug products, including those for a natural product, a recombinant DNA-derived protein/polypeptide, or a complex or conjugate of a drug substance with a monoclonal antibody, required a prior approval supplement (previous

§ 314.70(b)(1)(iv) and (b)(2)(v)). FDA has reduced the reporting category for many manufacturing process changes relating to these products by allowing them to be reported in changes-being-effected supplements or annual reports. However, the three changes specified in this provision, which are unique to these specific types of drugs, are considered to have a substantial potential to adversely affect the identity, strength, quality, purity, or potency of the drug product as they may relate to the safety or effectiveness of a drug product. Virus or adventitious agent removal or inactivation processes are the means by which FDA ensures that adventitious agents such as porcine parovirus, if present, are removed. Failure to remove such adventitious agents has a significant potential to adversely affect public safety. Changes in source material or cell line and establishment of a new master cell bank or seed have a substantial potential to affect the quality of a drug substance. For example, a change in source material (e.g., species, geographic region of harvesting) could result in different impurities or contaminants (e.g., pesticides) than were previously seen or a change in potency.

Proposed § 314.70(b)(3) stated that the applicant must obtain approval of a supplement from FDA before distributing a product using a change and specified the information to be included in the supplement.

(Comment 50) A few comments requested adding "as appropriate" as follows: "Except for submissions under paragraph (e) of this section, the following shall be contained in the supplement, as appropriate." The comments said that not all listed material is relevant for every submission.

FDA declines to revise the provision as requested. FDA expects that the information specified in § 314.70(b)(3)(i) through (b)(3)(v) will be needed for almost all supplemental applications. FDA believes that the addition of "as

appropriate" may incorrectly give the impression that this information is not routinely needed and would result in supplemental applications being submitted with insufficient information. FDA may specify in a guidance that information required in § 314.70(b)(3)(i) through (b)(3)(v) is not needed for a particular change. However, in the absence of such a recommendation, FDA would expect § 314.70(b)(3)(i) through (b)(3)(v) to be addressed in each supplemental application. The information in § 314.70(b)(3)(vi) and (b)(3)(vii) is needed only in certain situations, and this is clearly indicated.

Proposed § 314.70(b)(3)(vi) stated that for a natural product, a recombinant DNA-derived protein/polypeptide product, or a complex or conjugate of a drug with a monoclonal antibody, relevant validation protocols must be provided in addition to the requirements in § 314.70(b)(3)(iv) and (b)(3)(v).

(Comment 51) One comment said that the requirement that relevant validation protocols be provided is overly restrictive and burdensome. The comment suggested that this statement be rephrased to state "validation protocols may be requested by the FDA." Another comment recommended that this section be deleted because there is no need for different requirements for these products. The comment said that this information (relevant validation protocols) is available for review onsite. The comment said that if FDA disagrees and feels that special requirements are warranted, the comment recommended these specific details be more appropriately captured in the guidance instead.

Unless otherwise specified by FDA, validation protocols and data need not be filed in the application, ~~but should be retained at the facility and be available for review by FDA at the agency's discretion.~~ For most products, FDA does not require the submission of validation protocols and data. However,

OMB

for a natural product, a recombinant DNA-derived protein/polypeptide, or a complex or conjugate of a drug substance with a monoclonal antibody, FDA does require the submission of validation protocols for certain critical manufacturing processes unique to these drug substances and drug products. For example, FDA would expect the validation protocol for the virus or adventitious agent removal or inactivation process to be submitted in an application. FDA currently requires this type of information to be submitted in an application and believes it is necessary; therefore, FDA declines to revise the regulation as suggested.

Proposed § 314.70(b)(3)(vii) stated that for sterilization process and test methodologies, relevant validation protocols must be provided in addition to the requirements in § 314.70(b)(3)(iv) and (b)(3)(v).

(Comment 52) One comment said that the inclusion of validation protocols for sterilization assurance is new. The comment also said that submitting all validation data is different from data summaries previously requested and provided for microbiological consults.

FDA disagrees with this comment. The information on sterility assurance FDA expects an applicant to provide in an application and the format of the data are described in the guidance entitled "Submission of Documentation of Sterilization Process Validation in Applications for Human and Veterinary Drug Products." The provisions of § 314.70(b)(3)(vii) are consistent with current FDA policy.

(Comment 53) One comment said that clarification is needed that the test methodologies and validation protocols referred to in this section are for the sterilization process only.

FDA agrees and has replaced "test methodologies" with "test methodologies related to sterilization process validation" in new § 314.70(b)(3)(vii).

Proposed § 314.70(b)(3)(viii) stated that a reference list of relevant SOPs, when applicable, must be contained in the supplement.

(Comment 54) Many comments recommended that reference to SOPs be deleted. Several of these comments said that it was unclear what value a reference list of SOPs provides in the division review process and that SOPs are generally considered a CGMP issue. One comment said that reference to appropriate SOPs is currently required only as it pertains to sterilization processes and biologic products. The comment also contended that inclusion of a reference list of SOPs in the submission for any type of change is not necessary. Several comments said that "when applicable" was too vague and one comment recommended that the provision be revised to state "A reference list of relevant standard operating procedures (SOPs) for aseptic processing operations."

An applicant is required to submit a "full description of controls used for the manufacture, processing, and packing of a drug" (section 505 of the act). This information may be submitted in different forms, including SOPs. In most cases, SOPs do not include information relevant to the NDA or ANDA review, but rather information relevant to determining an applicant's compliance with CGMPs. However, in the case of a natural product, a recombinant DNA-derived protein/polypeptide, a complex or conjugate of a drug substance with a monoclonal antibody, or a sterilization process, information contained in SOPs is often relevant to the review of certain aspects of an application. FDA has deleted proposed § 314.70(b)(3)(viii) and revised § 314.70(b)(3)(vi) and

(b)(3)(vii) to limit the need for information on SOPs in these situations. The agency clarifies that information regarding SOPs is needed in some cases. FDA wishes to emphasize that while the information is needed for the application review, it is not always necessary to submit the actual SOP as long as the required information is provided in sufficient detail as part of the application.

On its own initiative, FDA has revised § 314.70(b)(3)(iv) by replacing the phrase "evaluate the effect of the change * * * (validating the effects of the change)" with "assess the effects of the change" because the term is defined at § 314.3(b). In the introductory text of § 314.70(b)(3), FDA replaced the phrase "the following shall" with "the following information must" to add clarity.

Proposed §§ 314.70(b)(4) and 601.12(b)(4) provided that an applicant may request an expedited review of a supplement if a delay in making the change would impose an extraordinary hardship or for public health reasons.

(Comment 55) One comment said that a complete definition of expedited review from FDA's "Manual of Policies and Procedures" (MAPPs) should be incorporated in the regulation. One comment said FDA should consider adding mandatory vendor-imposed changes (without sufficient reaction time) to the list of "not reasonably foreseen" events.

FDA has published two MAPPs on expedited review—MAPP 5420.1 entitled "Requests for Expedited Review of Supplements to Approved ANDAs and AADAs" and MAPP 5410.3 entitled "Requests for Expedited Review of NDA Chemistry Supplements." These MAPPs contain criteria that FDA uses in granting expedited review based on public health need, extraordinary hardship on the applicant, or agency need. FDA declines to add this detailed information on internal FDA procedures to the regulation but encourages applicants to review these MAPPs to see how FDA would assess a request for

an expedited review. The MAPPs already include "abrupt discontinuation of supply of active ingredient, packaging material, or container closure" as an example of an extraordinary hardship that was not reasonably foreseen. An applicant is required to submit sufficient documentation to support a need for an expedited review. In the case of an abrupt discontinuation of supply, FDA will require information to support that the discontinuation was abrupt such as when the supplier informed the applicant of the discontinuation of supply, the amount of supplies available in-house and from the supplier, and the date the supplies are expected to run out. FDA emphasizes that inadequate planning on the part of an applicant is not a reason for FDA to expedite the review of a supplement based on extraordinary hardship.

(Comment 56) A few comments requested that FDA provide feedback to the sponsor on acceptance or refusal of an "expedited review" request within 30 days.

FDA's MAPPs 5240.1 and 5310.3 describe procedures for processing expedited review requests. All requests for expedited review are reviewed promptly, usually within 30 days of receipt. If the review division denies the request, the applicant will be contacted. FDA declines to specify that it will contact applicants to advise them that their expedited review request has been granted or that the decision will be made within 30 days. However, applicants can contact the review division at any time about the status of their request.

E. Changes Requiring Supplement Submission at Least 30 Days Prior to Distribution of the Drug Product Made Using the Change (Moderate Changes)

Proposed § 314.70(c)(1) required that a supplement be submitted for any change in the product, production process, quality controls, equipment, or facilities that has a moderate potential to have an adverse effect on the identity,

strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product. If the change concerns labeling, 12 copies of the final printed labeling must be included.

(Comment 57) One comment said that in the preamble to the final rule, FDA should further clarify the criteria to be used to distinguish between changes-being-effected supplements that can be implemented immediately and those where distribution cannot occur until 30 days after FDA receives the supplement.

The decision by FDA as to whether a moderate change should be classified as one that can be implemented by an applicant when FDA receives a supplement or one requiring supplement submission at least 30 days prior to distribution of the drug product made using the change depends on many factors. Some of these factors include the need for FDA to verify compliance status, dosage form, route of administration, or whether, based on FDA's experience, a particular type of change is usually complete and provides the proper information. It is not possible to provide a general list of factors considered because different factors are considered by FDA for each type of change.

(Comment 58) A few comments requested changes in the format of this section. One comment said that supplements for changes being effected in 30 days as well as changes being effected immediately are defined as "moderate changes." The comment asked whether there can be different verbiage for these two categories to allow differentiation. Another comment suggested that the two types of changes-being-effected supplements should be separated into different paragraphs under this section.

FDA declines to revise the regulations as requested. FDA believes that the format and terms are adequate and will not be unclear when individuals become more familiar with the regulations and the guidance.

(Comment 59) One comment said it recognizes that the supplements for changes being effected in 30 days is a statutory classification. The comment said that, unfortunately, the provision does not provide material advantage over a changes-being-effected supplement for either the agency or the industry, especially for new chemical entities (NCEs). The comment said that, instead, the provision adds a 30-day wait period that does not currently exist for NCEs. The comment said that, from FDA's point of view, the reviewer will be spending twice the amount of time on the same application, first for an administrative review for the completeness of the information and later to actually review the application. The comment said that from industry's point of view, the 30-day wait period does not necessarily provide increased assurance of an approval action. The comment suggested that any change that can be the subject of a changes-being-effected-in-30-days supplement could just as easily be reclassified as a changes-being-effected supplement. The comment said that this would save time for both FDA and industry.

FDA declines to revise the regulation as requested. The changes-being-effected-in-30-days provision allows certain changes previously requiring prior approval to be implemented rapidly, thus reducing the percentage of supplements requiring prior approval. FDA recognizes that the public health can be adequately protected without requiring approval of certain manufacturing changes prior to distribution of the product made with the change. FDA continues to believe that it is important that such changes be documented and validated so there is a mechanism for assessing the

consequences of the changes and that the agency approve such changes. Ready access to information regarding such changes through submission of a supplement 30 days before distribution of the product would protect against the distribution of unsafe or ineffective products while speeding the availability of improved products. The provision is intended to benefit the public health because it permits FDA to stop or delay a product from being distributed to the public when the product is made with a major change (i.e., one with a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product) that is improperly categorized as a moderate change. The provision also permits the agency to act when information necessary to demonstrate that the change has not adversely affected product quality is not provided.

(Comment 60) Several comments recommended inserting "only" in the last sentence to read: "If the change concerns only labeling, include 12 copies of final printed label." One comment said that there are changes that have minor impacts on labeling (for example, signature changes) that, if implemented as stated, would result in an increased regulatory burden to provide finished product labeling prior to change implementation.

FDA declines to revise the regulation as requested because changes-being-effected supplements (within 30 days and immediately) that include both manufacturing changes and labeling changes must also include 12 copies of the final printed labeling, if appropriate. However, FDA has clarified that the only labeling changes that require submission of 12 copies of finished product labeling at the time of supplement submission are those classified as a moderate change. Changes-being-effected manufacturing supplements that

result in labeling changes that are classified as minor under § 314.70(d) do not have to include copies of final printed labeling. The final printed labeling for these minor labeling changes can be submitted in the next annual report in accordance with § 314.81(b)(2)(iii).

FDA has clarified § 314.70(c)(1) to explain when final printed labeling must be submitted by revising the last sentence to read "If the supplement provides for a labeling change under paragraph (c)(6)(iii) of this section, 12 copies of the final printed labeling must be included."

(Comment 61) One comment said that FDA should delete the requirement to provide 12 copies of the final printed labeling with a changes-being-effected labeling supplement. The comment said that although the specified changes may be submitted in a changes-being-effected supplement, at times they may not be implemented until after the submission. The comment said that to print final labeling specifically for the changes-being-effected supplement is unnecessarily expensive and complicates the normal labeling printing process. The comment said that an alternative would be to submit a typed copy of the labeling and submit the final printed labeling in the annual report.

FDA declines to revise the regulation as requested. Moderate labeling changes, which are those that have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product, can be implemented immediately without FDA's prior approval. In FDA's experience, errors that occurred when draft labeling was converted to final printed labeling have made the final printed labeling unacceptable. Also, FDA reviews not only the content of labeling for accuracy but also the format (e.g., layout, size of print) for clarity. A typed copy of the labeling does not always accurately

reflect the format of the final printed labeling. The labeling should be available for review at the time of submission whether or not the applicant intends to implement the change immediately upon FDA receipt of the supplement.

(Comment 62) One comment stated that current § 314.70(c)(3) permits a different facility to be used for the production of the drug substance under certain conditions. The comment said that the proposal does not include this provision, and that FDA intends to provide recommendations concerning this in certain guidance documents. The comment said that this provision of current § 314.70 should be retained in the revised regulation because the industry is familiar with the provision and has used it for years.

FDA declines to revise the proposal as requested. As stated in the proposal, the agency's approach is to issue regulations that set out broad, general categories of manufacturing changes and use guidance documents to provide FDA's current thinking on the specific changes included in those categories. FDA has provided recommendations on changes in manufacturing sites in FDA's guidance entitled "Changes to an Approved NDA or ANDA."

Proposed § 314.70(c)(2)(i) stated that changes requiring supplement submission at least 30 days prior to distribution of the drug product made using the change (moderate changes) includes the following change: A change in the container closure system that does not affect the quality of the final drug product.

(Comment 63) Many comments recommended that the requirement should be changed to include "significant change" and/or "adversely affect," so that the regulation would read: "A significant change in the container closure system that does not adversely affect the quality of the final drug product."

FDA declines to revise the provision as requested. New § 314.70(c)(1) already states that the changes that should be filed in changes-being-effected supplements are those that have a moderate potential to have an "adverse effect." Adding the word "adversely" to this provision is redundant. Adding the term "significant" is also inappropriate because any change, whether big or small, should not adversely affect the quality of the final drug product. Some manufacturing changes have an adverse effect on the identity, strength, quality, purity, or potency of the drug product. In many cases, the applicant chooses not to implement these manufacturing changes, but sometimes the applicant wishes to do so. If an assessment indicates that a change has adversely affected the identity, strength, quality, purity, or potency of the drug product, the change should be submitted in a prior approval supplement, regardless of the recommended reporting category for the change. For example, a process change recommended for a changes-being-effected-in-30-days supplement could cause the formation of a new degradant that requires qualification and/or identification. The applicant may believe that there are no safety concerns relating to the new degradant. Even so, the applicant should submit this change in a prior approval supplement with appropriate information to support the continued safety and effectiveness of the product. During the review of the prior approval supplement, FDA will assess the impact of any adverse effect on the drug product as this change may relate to the safety or effectiveness of the drug product.

(Comment 64) One comment noted an apparent conflict between proposed § 314.70(b)(2)(vi), which stated that a "change in a container closure system that * * * may affect the impurity profile of the drug product" should be filed in a prior approval supplement, and proposed § 314.70(c)(2)(i), which stated

that "a change in the container closure system that does not affect the quality of the final drug product" should be filed in a changes-being-effected-in-30-days supplement. The comment said that this would allow for inconsistent and overly conservative interpretations of what might fall under § 314.70(b)(2)(vi).

FDA agrees and has clarified the wording in these two provisions. Changes to proposed § 314.70(b)(2)(vi) were discussed previously under section III.C of this document. For consistency, § 314.70(c)(2)(i) was revised to exclude changes that would be included under § 314.70(b) and (d).

FDA emphasizes that the container closure system and packaging component changes identified in § 314.70(b) must be filed in a prior approval supplement even if an applicant concludes that the quality of the drug product has not been adversely affected. The provision has also been revised to standardize terminology, as requested, by changing "final drug product" to "drug product."

Proposed § 314.70(c)(2)(ii) stated that changes requiring supplement submission at least 30 days prior to distribution of the drug product made using the change (moderate changes) included the following change: Changes solely affecting a natural protein product, a recombinant DNA-derived protein/polypeptide product or a complex or conjugate of a drug with a monoclonal antibody, including the following: (1) An increase or decrease in production scale during finishing steps that involves new or different equipment; and (2) replacement of equipment with that of similar, but not identical, design and operating principle that does not affect the process methodology or process operating parameters.

(Comment 65) Several comments said that having special requirements for this category of products represents additional regulatory reporting requirements beyond current practice. A few comments recommended that this section be deleted. One comment said that these products should not be regulated differently than the traditional products. The comment said that if FDA disagrees and feels that this requirement is warranted, the specific details be captured in the guidance instead.

FDA declines to revise the regulation as requested. There are specific issues and concerns relating to the production of proteins that are not routinely associated with other classes of drugs; therefore, FDA has specified certain requirements for proteins. Proteins are susceptible to denaturation. Denaturation can be caused by changes in sheer force as a result of scale and/or equipment changes. Also, proteins differentially adsorb to surfaces. The identity, strength, quality, purity, or potency of the product could be affected by changes in scale or equipment because of these characteristics.

(Comment 66) A few comments requested that FDA clarify whether this section applies to drug products or drug substance.

FDA agrees and has clarified the proposed language, which is intended to apply to both drug substance and drug product.

(Comment 67) A few comments recommended that FDA delete reference to "natural protein products." The comments also requested clarification as to whether the definition natural products includes fermentation products.

FDA declines to revise the regulation as requested. Issues about scale and equipment and concerns associated with proteins are the same whether the protein is derived from a natural source or by other means, such as DNA

technology. The definition of natural products was discussed in comment number 48 of this document. Natural proteins are a subset of natural products.

(Comment 68) One comment said that this section applies to both an increase and decrease in batch size involving new equipment. The comment asked whether new equipment includes replacement equipment.

FDA agrees and has clarified the proposed language. The phrase "new or different equipment" has been replaced by the phrase "different equipment." Different equipment can include new models, changes in capacity, construction materials (e.g., glass-lined tanks to stainless steel), equipment design, and/or equipment operating principles. If a scale change involves replacing equipment with equipment that is identical in all critical aspects (e.g., same model and capacity, same construction materials), this is a type of change that could be reported in an annual report. For the same reasons, FDA is revising § 601.12(c)(2)(ii) to delete the word "new."

(Comment 69) A few comments requested clarification of "finishing steps."

FDA declines to revise the regulations to provide clarification of the term "finishing steps." In general, finishing steps are considered those steps in the manufacturing process where the stability, or the property and performance, of a protein product is less likely to be affected by changes in scale or equipment. The steps in a manufacturing process that would be considered finishing steps depend on the manufacturing process and the specific protein being manufactured. A particular manufacturing step may be considered a finishing step for one product but not for another. An applicant is encouraged to discuss with FDA which steps would be considered finishing steps for a

particular product and process. This discussion should occur as early in the process as possible, including during investigational new drug (IND) meetings.

(Comment 70) A few comments requested clarification of the difference between equipment that is "similar but not identical," proposed as a changes-being-effected-in-30-days supplement, and the SUPAC terminology of equipment of the "same design and operating principle," which is already defined in the SUPAC guidances and the June 1999 proposal as an annual report change. The comment said that the difference is not readily apparent and may lead to varying interpretations of regulatory submission requirements. The comments said that for equipment changes that are of different operating principle and design, FDA should consider the major change category, and for equipment changes that are of the same operating principle but different design, FDA should consider the moderate change category.

FDA agrees and has clarified the requirement by replacing the phrase "of similar, but not identical, design and operating principle that" with the phrase "that of a different design that." Equipment of a different design may or may not have a different operating principle.

(Comment 71) One comment suggested inserting the word "adversely" before "affect" to read: "Replacement of equipment with that of similar, but not identical, design and operating principle that does not adversely affect the process methodology or process operating parameters." The comment said that replacement of equipment that does not adversely affect the process methodology or operating parameters and/or positively affects process methodology or operating parameters should be reported as a minor change.

FDA declines to revise the provision as requested. New § 314.70(c)(1) already states that the changes that should be filed in changes-being-effected

supplements are those that have a moderate potential to have an "adverse effect." Adding the word "adversely" to this provision is redundant.

Proposed § 314.70(c)(4) stated that pending approval of the supplement by FDA, except as provided in paragraph (c)(6), distribution of the product made using the change may begin not less than 30 days after receipt of the supplement by FDA. The information listed in § 314.70(b)(3)(i) through (b)(3)(viii) must be contained in the supplement.

(Comment 72) One comment said that the last sentence in § 314.70(c)(4) should be revised to read: "The information listed in paragraphs (b)(3)(i) through (b)(3)(vii) * * *" because currently CGMP validation information, including a reference to appropriate SOPs, is required to be submitted in applications only as it pertains to sterilization processes.

FDA has revised § 314.70(c)(4) to make it consistent with the changes made in § 314.70(b)(3) to address the concerns raised by the comment (see discussion in comment numbers 50 through 54 in section III.C of this document) and also to clarify the term "product."

(Comment 73) One comment said that a time line and dispute resolution process needs to be defined by regulation or guidance in case of disputes regarding the type of information needed to support a change.

FDA does not believe it is necessary to revise proposed § 314.70 to address this issue. Actions by reviewers or other Center officials may be appealed through the appeals mechanism already in place in each Center to the Center Director and, ultimately, to the Commissioner of Food and Drugs. Dispute resolution procedures are detailed in 21 CFR 10.75 and 21 CFR 312.48, and §§ 314.103 and 601.12(h). FDA has also provided additional information in guidance documents. In the **Federal Register** of March 7, 2000 (65 FR 12019),

FDA issued a guidance entitled "Formal Dispute Resolution; Appeals Above the Division Level." The guidance describes the mechanism for resolution of procedural (including administrative) and scientific disputes in CDER and CBER.

Proposed § 314.70(c)(5) stated that the applicant must not distribute the product made using the change if, within 30 days following FDA's receipt of the supplement, FDA informs the applicant that either: (1) The change requires approval prior to distribution of the product in accordance with paragraph (b); or (2) any of the information required under § 314.70(c)(4) is missing. The applicant must not distribute the product made using the change until FDA determines that compliance is achieved.

(Comment 74) One comment said that if FDA determines within 30 days of receipt of the supplement that the change is properly submitted but the required information is incomplete, the applicant would be required to supply the missing information and wait until FDA determines that the supplement is in compliance before distributing the product. The comment contended that as long as the firm submits the data requested by FDA, it should be able to go to market and not wait until FDA determines that the supplement is "in compliance," which could take months since FDA is not now bound by the 30-day requirement.

FDA agrees and has clarified the requirement based on this comment. FDA has revised § 314.70(c)(5) to provide that, in the case of missing information, the applicant must not distribute the drug product until the supplement has been amended to provide the missing information.

(Comment 75) One comment asked, when additional information is provided, whether FDA's determination of compliance with the requirements of this section is equivalent to an approval of the supplement.

FDA has revised this section, and this comment is no longer applicable. However, FDA clarifies that it sends a formal letter to an applicant stating that a particular supplement is approved and that no other communication from FDA should be construed as an approval.

Proposed § 314.70(c)(7) stated that if the agency disapproves the supplemental application, it may order the manufacturer to cease distribution of the drug products made with the manufacturing change.

(Comment 76) A few comments recommended that FDA replace this requirement with the following: "If FDA later determines that the supplemental application is not immediately approvable, the agency will work with the applicant to resolve all issues and to assure the continued availability of the drug." Another comment recommended that this requirement be limited to only those cases where an adverse effect on safety or efficacy can be demonstrated. One comment said that although this is the language contained in section 506A(d)(3)(B)(iii) of the act, it is a reversal of long-time FDA policy of allowing firms to respond to deficiencies and get the supplement approved without interfering with distribution. The comment said that FDA should continue its long-standing policy.

FDA declines to revise the provision as requested. The regulation is consistent with section 506A(d)(3)(B)(iii) of the act. There may be some instances where FDA determines, after the drug product made using the change has been distributed, that the information submitted in the supplement fails to adequately demonstrate the continued safety and effectiveness of the drug

product. In such cases, FDA will make all possible efforts to resolve problems with the applicant concerning the supplement submission without requiring the removal of the drug product from the marketplace. In cases where FDA determines that there may be a danger to public health due to continued marketing of the drug product or when FDA determines that the issues may not otherwise be resolved, the agency may require that the applicant cease distribution of the drug product made using the change or that the product be removed from distribution pending resolution of the issues related to the change.

(Comment 77) One comment said that if FDA disapproves a changes-being-effected-in-30-days supplement, the sponsor should be notified within 30 days of this submission as stated in § 314.70(c)(5)(ii).

FDA declines to revise the regulation based on this comment. FDA intends during the 30-day period to focus its review on determining whether the applicant reported the change using the appropriate mechanism and, if so, whether any of the required information is missing. FDA intends to perform the substantive review of the submission as expeditiously as possible, but this is unlikely to occur within 30 days of receipt of the supplement.

F. Changes For Which Distribution of the Drug Product Involved May Commence When FDA Receives a Supplement (Moderate Changes)

Proposed § 314.70(c)(6) stated that FDA may designate a category of changes for which the holder of an approved application making such a change may begin distribution of the drug upon receipt by FDA of a supplemental application for the change. These changes include, under § 314.70(c)(6)(i), an addition to a specification or changes in the methods or controls to provide increased assurance that the drug will have the characteristics of identity,

strength, quality, purity, or potency that it purports or is represented to possess.

(Comment 78) Several comments recommended that an addition to a specification or change in the methods or controls to provide increased assurance that the drug will have the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to possess should be considered to have a minimal potential to have an adverse effect and should be allowed to be filed in the annual report.

FDA declines to revise the regulation as requested. FDA has identified certain specific changes that provide increased assurance that may be submitted in an annual report, such as the tightening of an acceptance criterion. However, this is a general provision and the assessment of whether or not a change provides "increased assurance" is subjective and must be supported by studies and data, as appropriate. FDA must have the opportunity to concur with an applicant's assessment that a change provides "increased assurance" in a timely manner. Reporting of such changes in an annual report would not afford FDA this opportunity because a change may be in effect for up to a year before FDA would have the opportunity to review the change. Changes that do not necessarily provide increased assurance may be a type of change that must be submitted in a changes-being-effected-in-30-days supplement or a supplement that requires approval prior to distribution of the product made using the change.

(Comment 79) One comment recommended that FDA change "addition to a specification or changes in the methods or controls" to "addition to a specification or changes in the tests, analytical procedures, or acceptance criteria."

FDA declines to revise the regulation as requested. The phrase "methods or controls" is not used by FDA to mean tests, analytical procedures, or acceptance criteria. Methods and controls relate to the manufacturing process.

Proposed § 314.70(c)(6)(ii) included the following category: A change in the size and/or shape of a container for a nonsterile drug product, except for solid dosage forms, without a change in the labeled amount of product or from one container closure system to another.

(Comment 80) A few comments recommended adding "a sterile drug product, or a sterile drug substance" to read "* * * container for a nonsterile drug product, except for solid dosage forms, a sterile drug product, or a sterile drug substance without a change." The comments said that changes in the size and shape of containers for sterile drug substances or sterile drug products have only moderate potential impact. The comments said that this is especially true when the nature of the size/shape changes are very minor, as is often the case when suppliers make minute adjustments in their packaging components.

FDA declines to revise the regulation as requested. As discussed in the comments for § 314.70(b)(2)(iii) in section III.C of this document, sterility of drug products or drug substances is a fundamental and essential quality attribute of these drugs and is a critical aspect of the safety assessment. Changes in the container closure system, even if minimal, may affect the sterility assurance of the drug product and are a major change. For sterile drug substances, the effect of changes in the size and/or shape of the container closure system is considered by FDA to be of lower risk because of the differences in procedures for sterilizing drug substances and drug products, but the risk is still higher than for nonsterile products. Therefore, FDA declines to specify in the regulations that these changes can be submitted in a changes-

being-effected supplement. Additional information on changing container closure systems for sterile drug substances or drug products is included in the guidance "Changes to an Approved NDA or ANDA."

(Comment 81) Several comments pertained to the phrase "without a change in the labeled amount of product." The comments said that proportional changes (i.e., ratio of the amount of drug product to size of container) are not expected to adversely affect the drug product, and one of these comments recommended that FDA should add "and a change in the labeled amount of product as long as the size of the container/closure system is changed proportionally." Other comments said that a corresponding change in fill quantity, along with a change in container size, is expected and readily acceptable and that it is illogical to assume that a change in the amount of product would present any greater risk than a change in container size.

FDA declines to revise the regulation as requested or with similar language included in § 314.70(d)(2)(iv). The phrase "labeled amount of product" refers to the total quantity of drug product (e.g., milliliters, grams). FDA has included the phrase "without a change in the labeled amount of product" because of the agency's concern about the proliferation of unit-of-use containers that may invite the misuse of drug products. A unit-of-use container is one that contains a specific quantity of a drug product and that is intended to be dispensed to the patient without further modification except for the addition of appropriate labeling. Although few in number, some drug products may cause life-threatening side effects, such as permanent liver damage, if used for longer periods of time than recommended in the labeling. Similarly, certain drugs must be used for a specific length of time (e.g., antibiotics) or the treatment may be ineffective. Unit-of-use containers that contain a quantity of drug

product that invite underuse or overuse of the product as recommended in the labeling may be a public health risk. FDA considers changes in the labeled amount of a nonsterile drug product in a unit-of-use container to have a moderate potential to adversely affect the safety and efficacy of the drug product and expects that these changes would normally be submitted in a changes-being-effected-in-30-days supplement under § 314.70(c)(2)(i). This would give FDA an opportunity to raise a concern about a package presentation prior to distribution of the product.

FDA's concern is less when the "labeled amount of product" is changed in multiple-unit containers for nonsterile drug products. FDA considers this change to have the same level of risk as a change in the size and/or shape of the container. A multiple-unit container is a container that permits withdrawal of successive portions of the contents without changing the strength, quality, or purity of the remaining portion. This type of container is not for direct distribution to patients, but is used by health care practitioners who dispense the drug in smaller amounts in accordance with a physician's instructions. While FDA declines to revise the regulations to specify the distinction between unit-of-use and multiple-use containers because of the complexity of the issue, FDA will address this issue when revising the guidances "Changes to an Approved NDA or ANDA" and "Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products."

Proposed § 314.70(c)(6)(iii)(C) included as a moderate change a change in the labeling to add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the product.

(Comment 82) One comment said that FDA should replace the words "and administration" in § 314.70(c)(6)(iii)(C) with the words "administration and storage."

FDA declines to revise the regulation as requested. The addition or strengthening of a storage statement could reflect a change in the expected characteristics or quality of a drug product and would be a major change. Also, one of FDA's objectives is to have the same drug products stored similarly to avoid confusion in the marketplace. FDA would need to review the proposed change prior to implementation to determine if: (1) The change is appropriate, (2) any changes in product quality causing the labeling change significantly impact the safety or effectiveness of the drug, and (3) there are other issues that need to be addressed either on an individual company basis or globally.

Proposed § 314.70(c)(6)(iii)(E) included as a moderate change any other change specifically requested by FDA.

(Comment 83) One comment said that any changes made to the labeling that are specifically required by the FDA should be reportable in the annual report.

FDA declines to revise the June 1999 proposal as requested but has revised § 314.70(c)(6)(iii)(E) to provide clarification. As stated in the June 1999 proposal, FDA proposed adding this section to allow labeling changes that normally require prior approval to be submitted in a changes-being-effected supplement when FDA specifically requests the change. FDA has clarified § 314.70(c)(6)(iii)(E) as follows: "Any labeling change normally requiring a supplement submission and approval prior to distribution of the drug product that FDA specifically requests be submitted under this provision." FDA has

also clarified § 601.12(f)(2)(i)(E) as follows: "Any labeling change normally requiring a supplement submission and approval prior to distribution of the product that FDA specifically requests be submitted under this provision."

G. Changes To Be Described in the Next Annual Report (Minor Changes)

Proposed § 314.70(d)(1) required that changes in the product, production process, quality controls, equipment, or facilities that have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product must be documented by the applicant in the next annual report in accordance with § 314.81(b)(2).

Proposed § 314.70(d)(2)(i) required the following change to be documented in the next annual report: Any change made to comply with an official compendium that is consistent with FDA requirements and provides increased assurance that the drug will have the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to possess.

FDA received 18 comments on this provision. Fifteen comments requested that FDA change this requirement to read "Any change to comply with an official compendium;" two comments requested that FDA change this requirement to read "Any change made to comply with an official compendium that is consistent with FDA requirements;" and one comment did not provide a suggested revision.

FDA declines to revise the provision as requested in the comments but has revised the provision to provide further clarification. The basis for this decision is discussed below. The majority of the comments pertained to drugs regulated under, and the statutory requirements regarding official compendia included in, the act. Therefore, FDA has responded to the comments from this

perspective. FDA has made corresponding changes to § 601.12(c) and (d) for biologics regulated under section 351 of the PHS Act.

(Comment 84) Many comments said that the proposal to require supplemental applications for some changes that are made to comply with an official compendium fails to recognize the legal status of the USP/NF under the act and undermines the authority of the USP/NF as official compendia and sources of standards. One comment stated that if a drug product meets compendial requirements, it is considered unadulterated under the act. Another comment stated that the USP is the responsible compendial body for regulatory specifications.

Under section 501(b) of the act (21 U.S.C. 351(b)), a drug that is recognized in an official compendium may be considered adulterated if its strength differs from, or its quality or purity fall below, the standards set in the compendium. Determinations of adulteration under this provision of the act must be made in accordance with the analytical procedures set in the compendium. When there is no analytical procedure prescribed in the compendium or the tests prescribed in the compendium are insufficient, the agency can follow the process outlined in the statute and issue a regulation to provide an appropriate analytical procedure. As stated in the act, no drug defined in an official compendium will be considered adulterated under section 501(b) of the act because its strength differs from, or its quality or purity fall below, the standards set in the compendium if the differences from the standard are stated in its label. Under section 502(g) of the act (21 U.S.C. 352), a drug that is recognized in an official compendium may be considered misbranded if the drug is not packaged and labeled as prescribed in the compendium.

The agency is aware of the legal status of the USP/NF under the act as a standard for determining whether a drug may be considered adulterated or misbranded. A compendial product that fails to comply with USP/NF standards may be considered to be adulterated or misbranded under the act. However, a compendial product can still be considered adulterated or misbranded under other provisions of sections 501 or 502 of the act, even if it complies with USP/NF standards.

While the standards in the USP/NF are legally enforceable standards for determining whether a product is considered adulterated under section 501 of the act, these standards are not considered the complete regulatory specification. The agency is responsible for establishing regulatory specifications as part of the approval of an application. Under sections 505(b) and 505(j) of the act (21 U.S.C. 355(b) and 355(j)) , an application must include a full description of the methods used in and the facilities and controls used for, the manufacture, processing, and packing of the drug. If the specifications included in the description are considered inadequate to ensure and preserve the identity, strength, quality, purity, or potency of the drug, the agency will refuse to approve the application. Standards established by an official compendium may be inadequate for the purposes of approving an application under section 505 of the act. The USP acknowledges that:

While one of the primary objectives of the Pharmacopeia is to assure the user of official articles of their identity, strength, quality, and purity, it is manifestly impossible to include in each monograph a test for every impurity, contaminant, or adulterant that might be present, including microbial contamination. These may arise from a change in the sources of the material or from a change in the processing, or may be introduced from extraneous sources. Tests suitable for detecting such occurrences, their presence of which is inconsistent with applicable good

manufacturing practice or good pharmaceutical practice, should be employed in addition to the tests provided in the individual monograph.
(USP 25, General Notices, page 7).

Similarly, while the labeling requirements in the USP/NF are legally enforceable standards for determining whether a product is misbranded under section 502 of the act, use of these standards alone does not ensure compliance with the act. The USP states "articles in this Pharmacopeia are subject to compliance with such labeling requirements as may be promulgated by governmental bodies in addition to the Pharmacopeial requirements set forth for the articles." (USP 25, General Notices, page 12).

Not all compendial standards or changes in existing compendial standards are: (1) Adequate to ensure and preserve the identity, strength, quality, purity, or potency of the drug or (2) consistent with other requirements of the act. For example, a deletion of an impurity test may result in an inadequate standard for ensuring the purity of the drug. Therefore, the agency does not believe that all changes made to comply with an official compendium are of a type that should be reported in an annual report.

(Comment 85) Many comments stated that the phrases "which are consistent with FDA requirements" and "provides increased assurance that the drug will have the characteristics of identity, strength, quality, purity, or potency that it purports or is represented to possess" are unclear. Several comments stated that "consistent with FDA requirements" allows for individual review interpretations. Several comments said that deleting or widening a specification due to a change in the USP should be allowed in an annual report.

FDA concurs that the provisions regarding changes to comply with an official compendium should be clarified. Separate discussions of labeling,

analytical procedures, and acceptance criteria and test changes follow, along with a discussion of the phrase "consistent with FDA requirements."

Labeling: Under section 502(g) of the act, a drug recognized in an official compendium may be considered misbranded if the drug is not packaged and labeled as prescribed in the compendium. The method of packing may be modified with the consent of the agency. One comment stated that there would be confusion in the marketplace if compendial labeling changes were not instituted uniformly. The agency concurs that all labeling changes made to comply with an official compendium that are consistent with FDA requirements should be reported in an annual report. These changes have minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety and effectiveness of the product. Consistent labeling promotes the safe use of products and reduces confusion in the marketplace.

Analytical procedures: For compendial drugs, the determination of whether the drug is adulterated under section 501(b) of the act must be made in accordance with the analytical procedures set in the compendium except when no analytical procedure is prescribed in the compendium or the tests prescribed in the official compendium are insufficient. In these situations, the agency can follow the process outlined in the statute and issue a regulation to provide an appropriate analytical procedure. Because of the legal status of compendial analytical procedures in the act and other requirements relating to analytical procedures in the statute, the agency concurs that changes in analytical procedures to comply with an official compendium may be filed in an annual report, except for changes to comply with an official compendium that result in the deletion of a test or the relaxation of an acceptance criterion.

The agency wishes to emphasize that under FDA's CGMPs, the suitability of all analytical procedures, including compendial procedures, must be verified under actual conditions of use. For example, an assay analytical procedure where degradation products, impurities, or excipients interfere with the analysis is not considered an acceptable analytical procedure. The use of unacceptable analytical procedures, even if specified in an official compendium, can be considered a violation of the act. The agency also wishes to emphasize that a change from an approved analytical procedure that is capable of quantifying impurities to a compendial analytical procedure that cannot quantify impurities is in essence a deletion of an impurities test. This change of procedure should not be reported in an annual report, but should be reported as any other request for deletion of an approved test.

Tests and acceptance criteria: Under sections 505(b) and 505(j) of the act, an application must include a full description of the methods used in and the facilities and controls used for, the manufacture, processing, and packing of the drug. If the specifications included in the description are considered inadequate to ensure and preserve the identity, strength, quality, purity, or potency of the drug, the agency will refuse to approve the application. As previously discussed in this document, the standards established by an official compendium may be inadequate for approving an application under section 505 of the act.

As part of the detailed application review process and in accordance with section 505 of the act, FDA requires that the application include tests and acceptance criteria that the agency believes are necessary to ensure and preserve the identity, strength, quality, purity, and potency of the product. The specifications included in the application are legally binding upon the

applicant, and a product that fails to comply with the specifications included in the application can be considered an unapproved drug under section 505 of the act. Compendial standards are often used in evaluating the specifications proposed in the application. However, compendial standards must often be supplemented with additional tests, such as a specific test for impurities, to ensure the identity, strength, quality, purity, and potency of the drug. Also, the tests and acceptance criteria in an application are often approved without benefit of a compendial standard for a drug because no compendial standard has been established. Situations could arise where, for example, FDA requires tests and acceptance criteria for specific impurities as part of approval of an application. These impurities are not specified in an existing monograph or are not included in a monograph published subsequent to the approval of the drug. If FDA allowed all changes to comply with an official compendium to be included in an annual report, the applicant could interpret this provision as allowing them to delete the tests which were required as a condition of approving the application.

A change to relax an acceptance criterion or delete a test is considered a major change. The agency needs to review a request for this type of change in the context of a particular NDA or ANDA to determine if the change will adversely affect the identity, strength, quality, purity, or potency of the product. Changes such as these, when requested solely at the initiative of the applicant, must be filed in a prior approval supplement. Reporting these changes in an annual report is not appropriate. However, when a change to relax an acceptance criterion or delete a test is made to comply with a change to an official compendium, the change is considered to have a moderate potential to have an adverse effect on the identity, strength, quality, purity,

or potency of the product as these factors may relate to the safety and effectiveness of the product. The change is considered moderate because: (1) The change has been reviewed by an independent group that has the goal of promoting public health and (2) the agency has had the opportunity through the USP process of reviewing the proposed change in general, but not necessarily in the context of each individual application affected by the change. Based on these factors, the agency will require a changes-being-effected-in-30-days supplement for a change to relax an acceptance criterion or delete a test to comply with a change to an official compendium. A change made to comply with an official compendium that results in a tightening of an approved acceptance criterion or an addition of a test is considered a minor change and may be filed in an annual report.

(Comment 86) FDA proposed that changes to comply with an official compendium could be reported in an annual report only if they were consistent with FDA requirements. Several comments stated that "consistent with FDA requirements" allows for individual review interpretations.

FDA declines to delete this phrasing but wishes to clarify that the term requirements means the requirements of the act or the applicable provisions in the Code of Federal Regulations (CFR). An annual report or changes-being-effected-in-30-days supplement should not be used to implement a change to comply with an official compendium when that change is not consistent with other FDA statutory or regulatory requirements. An example of this is a change to a compendial analytical procedure, when a different analytical procedure is specified in the regulations (e.g., 21 CFR part 610) because the use of the compendial analytical procedure is not consistent with FDA regulations. Another example of this is a change to a compendial analytical procedure that

is proven not to be suitable under actual conditions of use because the use of such an analytical procedure, even if specified in an official compendium, is not consistent with CGMPs (21 CFR 211.194). If situations like this occur, applicants should contact the agency, inform them of the situation, and request advice.

For the reason discussed previously in this document, the agency is adding §§ 314.70(c)(2)(iii) and 601.12(c)(2)(iv) to require a changes-being-effected-in-30-days supplement for a relaxation of an acceptance criterion or deletion of a test to comply with an official compendium that is consistent with FDA statutory and regulatory requirements. The agency is revising § 314.70(d)(2)(i) as follows: "Any change made to comply with an official compendium, except a change described in paragraph (c)(2)(iii) of this section, that is consistent with FDA statutory and regulatory requirements." The agency is also revising § 601.12(d)(2)(i) as follows: "Any change made to comply with an official compendium, except a change described in paragraph (c)(2)(iv) of this section, that is consistent with FDA statutory and regulatory requirements."

(Comment 87) Several comments stated that a drug must comply with the compendial quality standards or it may be considered adulterated or misbranded. The comments went on to say that when the USP makes a change and a company cannot comply until FDA approves the change, the marketed drug in the intervening period technically may be misbranded or adulterated if it fails to meet the changed compendial requirements.

The agency wishes to clarify as part of this final rule the circumstances under which a supplemental application must be submitted for changes to comply with an official compendium. A supplemental application must be submitted only when the change involves a relaxation of an acceptance

criterion or deletion of a test. The standards for the drug will differ from the standards prescribed in the official compendium until the agency approves the change. However, under these circumstances, the drug as marketed will have tighter specifications or more testing will be performed than has been specified in the official compendium. Therefore, the drug will not fall below the standards set in the official compendium and would not be considered adulterated under section 501(b) of the act.

(Comment 88) One comment said that the proposed language implies that there may be separate and/or different requirements to fulfill USP and FDA criteria. Other comments said that the same product, from different applicants, should be held to the same standards.

As discussed previously in this document, while the specifications in an official compendium are legally enforceable standards under section 502(b) of the act for determining whether a product is considered adulterated, these standards may not be sufficient to ensure and preserve the identity, strength, quality, purity, and potency of the drug as required under section 505 of the act for approval to market a drug. Generally, FDA uses compendial standards in evaluating the specifications proposed in an application. However, compendial standards must often be supplemented with additional tests to ensure the identity, strength, quality, purity, or potency of the drug. Similarly, while the labeling requirements in USP/NF are legally enforceable standards for determining whether a product is misbranded under section 502(g) of the act, use of these standards alone does not ensure compliance with the act. The statutory requirements regarding compendial standards as well as other statutory requirements must be considered to ensure compliance with the act.

The requirements under sections 501(b) and 502(g) of the act for determining whether a product is adulterated or misbranded and of section 505 of the act for approving an application are applied consistently to all products. Under sections 505(b) and 505(j) of the act, the specifications included in the application must be considered adequate to ensure and preserve the identity, strength, quality, purity, and potency of the drug or else the agency must refuse to approve the application. However, this does not mean that the specifications approved in different applications for the same drug are identical. For example, different analytical procedures may be approved as long as the analytical procedures are appropriate and valid. Another example is that where solvents are used, the agency routinely and consistently requests tests and acceptance criteria for residual solvents. However, because different manufacturers use different solvents, the tests and acceptance criteria will vary depending on the solvents used. In all cases, the approved specifications will have been determined by the agency to be adequate to ensure and preserve the identity, strength, quality, purity, and potency of the drug.

(Comment 89) Many comments stated that FDA is involved in the USP revision process and should use this process to resolve any differences between compendial requirements and FDA requirements and ensure that compendial changes do not compromise safety and efficacy. Once this is accomplished, all changes to comply with a compendial change should be submitted in an annual report.

The USP process for developing or changing a monograph, general notice, or general chapter is an open process. Anyone who is interested in a particular issue has the opportunity to comment. FDA participates in many USP

activities, including joint committees and public forums, and has designated persons throughout the agency to act as liaisons to the USP.

FDA recognizes that public standards such as those instituted by the USP are beneficial. However, the USP is a nongovernmental organization that works independently from FDA, and FDA has no authority to stop USP from implementing a new or revised standard. FDA must ensure the identity, strength, quality, purity, and potency of drugs by requiring appropriate specifications. Compendial standards are not always sufficient to provide this assurance. Moreover, certain changes in a public standard, such as deletion of a test or relaxation of an acceptance criterion, cannot always be considered an improvement in the standard, nor is it always clear that the change will not lessen the assurance of the identity, strength, quality, purity, or potency of the products affected by the change. After review of a change such as these in the context of a specific NDA or ANDA, FDA may confirm that the change does not adversely affect the drug. However, allowing such a change to be documented in an annual report would not provide the opportunity for the agency to assess the effect of the change in a timely manner. FDA considers the provisions in the final rule necessary to ensure the safety and effectiveness of drugs.

(Comment 90) Several comments said that the proposed provision regarding changes to comply with an official compendium was inconsistent with the intent of the Modernization Act.

FDA disagrees with these comments. Section 506A of the act requires a change in the specifications in the approved application to be submitted in a supplemental application and approved by the agency prior to the applicant distributing the product affected by the change (section 506A(c)(2)(A) of the

act). The act does not distinguish between changes in compendial and noncompendial specifications. The act allows the Secretary to exempt by regulation or guidance the requirement that changes in specifications may be submitted in prior approval supplements. However, the act also requires the agency to establish the reporting category for a change based on the potential for the change to adversely affect the identity, strength, quality, purity, and potency of the drug as they may relate to the safety and effectiveness of the drug. The agency believes the provisions in the final rule regarding changes to comply with changes in an official compendium are consistent with the intent of the Modernization Act.

(Comment 91) One comment also said that the proposal was not consistent with the initiatives under the National Partnership for Reinventing Government (REGO), the National Technology Transfer and Advancement Act (the NTTAA) of 1995 and the Paperwork Reduction Act of 1995 (the PRA).

FDA disagrees with this comment. The comment states that one of FDA's goals under REGO is a more efficient drug development process and review process that will lower the development costs and reduce by an average of 1 year the time required to bring important new drugs to the American people. This REGO goal relates to initiatives for drugs prior to approval by FDA and is not pertinent to this rule. However, one REGO initiative was to reduce the number of manufacturing changes that require agency preapproval for biological products and FDA revised its regulations to achieve this goal (see the **Federal Register** of January 29, 1996 (61 FR 2739), and July 24, 1997 (62 FR 39890)). FDA supports the REGO objective to transform FDA into a customer-oriented, results-driven organization and believes that the final rule,

which reduces regulatory burden with respect to postapproval changes for both biological products and human drugs, achieves this objective.

The National Technology Transfer Act of 1995 (NTTAA) (Public Law 104–113, 15 U.S.C. 3701 (1996)) encourages the use of voluntary consensus standards by Federal agencies as a means to carry out policy objectives and puts into law the policies of OMB Circular A–119 (see the **Federal Register** of February 19, 1998 (63 FR 8546)). The standards set by USP/NF are not voluntary standards because the standards are recognized in sections 501 and 502 of the act for the purposes of determining if a compendial drug is adulterated or misbranded. Therefore, the NTTAA is not pertinent. FDA is authorized to cooperate with associations and scientific societies in the revision of the USP (21 U.S.C. 377). FDA is a committed participant in this endeavor and in developing other voluntary and nonvoluntary consensus standards.

The purposes of the PRA (44 U.S.C. 3501–3520) include minimizing paperwork for business resulting in collection of information for the government, ensuring the greatest public benefit from the information collected, and minimizing the cost to the government of the collection of information. Section 506A(b) of the act states that a drug made with a manufacturing change (whether a major manufacturing change or otherwise) may be distributed only if, before distribution of the drug as so made, the holder involved validates the effect of the change on the identity, strength, quality, purity, and potency of the drug as these factors may relate to the safety and effectiveness of the drug. Moreover, each supplemental application or annual report must contain such information as the Secretary determines to be appropriate and include the information developed by the applicant to

validate the effects of the change (sections 506A(c)(1), (d)(2)(A), and (d)(3)(A) of the act). The information that will be submitted to support a change is independent of the reporting category for the change. FDA will require the same type of information to be submitted to support a change in a compendial specification regardless of whether the change is reported in a supplemental application or annual report. There is no additional paperwork burden based solely on the designation of a reporting category for a particular change.

(Comment 92) Many comments said that requiring compendial changes to be reported in anything other than an annual report was an increase in regulatory burden over what has been done in the past. Several comments said that there has been no public discussion about any concerns with the previous policy to allow changes to comply with compendial changes to be filed in an annual report.

FDA recognizes that there has been confusion about the provision in previous § 314.70(d)(1) that allowed any change made to comply with an official compendium to be reported in an annual report. In the **Federal Register** of June 4, 1986 (51 FR 20310), FDA published a proposed rule to clarify and limit the types of compendial changes that could be made in an annual report. FDA was preparing to issue a final rule regarding this proposal when Congress initiated discussions about postapproval manufacturing changes. FDA delayed publishing the final rule and incorporated revisions regarding reporting of changes to comply with an official compendium into its proposed rule implementing section 506A of the act. The provisions in the final rule for changes made to comply with an official compendium might be viewed by some as an increase in burden over how FDA has been interpreting this regulation in the past. However, FDA believes that the provisions are necessary

and consistent with the requirements of section 506A of the act to establish a reporting category for a change based on the potential for the change to adversely affect the identity, strength, quality, purity, or potency of the drug product as they may relate to the safety and effectiveness of the drug product. As explained previously, the information that will be submitted to support a change is independent of the reporting category for the change. FDA will require the same type of information to be submitted to support a change in a compendial specification regardless of whether the change is reported in a supplemental application or annual report. There is no additional paperwork burden based solely on the designation of a reporting category for a particular change.

(Comment 93) One comment stated that changes made to comply with changes in an official compendium should not have to include all the information needed for noncompendial products. The comment went on to say that a full description of the test methods and limits should not be necessary and that the company should not have to submit data demonstrating the suitability of a compendial change for the drug product if the compendial change is for a test method change or other change not specifically affecting the quality or the morphology of the material in question.

As previously discussed in this document, under section 506A of the act, each supplemental application or annual report must contain the information that the agency has determined to be appropriate and must include the information developed by the applicant to validate the effects of the change. Guidance on the information that should be submitted to support compendial and noncompendial analytical procedures is available from FDA.

Under proposed § 314.70(d)(2)(ii), the following change was to be documented in the next annual report: The deletion or reduction of an ingredient intended to affect only the color of the product.

(Comment 94) One comment recommended changing the requirement to read "the deletion, reduction or replacement with a color previously used in other CDER/CBER approved products."

FDA declines to revise the regulation as requested. FDA believes that any recommendations it may make concerning notification in an annual report of changes involving replacement of colors are best handled in guidance documents so that the issues and conditions associated with such changes can be fully explained.

(Comment 95) One comment said that changes in formulation, regardless of the intended purpose of the ingredient, are more appropriately addressed in terms of percent change allowed at each level as delineated in the SUPAC guidances.

FDA agrees that the issues relating to changes in components and composition for specific dosage form drug products are better handled in guidance documents, where they can be discussed in detail, rather than in the regulations. FDA included this specific provision in the proposed regulations because this annual report change, with minor editing changes, has been in the regulation since 1985.

Under proposed § 314.70(d)(2)(iii), the following change was to be documented in the next annual report: Replacement of equipment with that of the same design and operating principles except for equipment used with a natural protein product, a recombinant DNA-derived protein/polypeptide product, or a complex or conjugate of a drug with a monoclonal antibody.

(Comment 96) Several comments suggested that FDA delete all words after "principles" to read: "Replacement of equipment with that of the same design and operating principles." One comment said that it is reasonable to report in an annual report replacement with equipment of the same design and operating principles for these (i.e., protein) products.

FDA declines to revise the regulation as requested but has revised it to provide clarity. As discussed in section III.D of this document in response to comments on "Changes Requiring Supplement Submission at Least 30 Days Prior to Distribution of the Drug Product Made Using the Change (Moderate Change)," changes to identical equipment used in the production of proteins could be reported in an annual report. However, a change to equipment of the same design and operating principle, but not identical equipment (e.g., capacity), is not considered a minor change for protein products.

FDA has revised § 314.70(d)(2)(iii) as follows: "Replacement of equipment with that of the same design and operating principles except those equipment changes described in paragraph (c) of this section."

(Comment 97) One comment said the replacement of equipment of the same design and operating principles should not have to be reported. The comment said that for consistency with the existing SUPAC guidances, only a SUPAC subclass (i.e., design) change should be reported.

FDA declines to revise the regulation as requested. FDA's requirement to report changes in equipment of the same design and operating principle in an annual report is consistent with the existing SUPAC guidances. In the future, FDA may issue guidance lessening the reporting requirements in this area for specific cases. However, because of the diversity of drug products and

manufacturing processes regulated, FDA is unable at this time to lower the requirements as suggested in the comments.

Under proposed §§ 314.70(d)(2)(iv) and 601.12(d)(2)(v), the following change was to be documented in the next annual report: A change in the size and/or shape of a container containing the same number of dosage units for a nonsterile solid dosage form, without a change from one container closure system to another.

(Comment 98) Several comments said that FDA should delete "containing the same number of dosage units." The comments said that proportional changes (i.e., ratio of the amount of drug product to size of container) are not expected to adversely affect the drug product, that a corresponding change in fill quantity, along with a change in container size, is expected and readily acceptable, and that it is illogical to assume that a change in the amount of product would present any greater risk than a change in container size.

FDA declines to revise the regulation as requested. As discussed in the response to comment 81 of this document, FDA is concerned about the proliferation of unit-of-use containers that may invite the misuse of drug products.

Under proposed §§ 314.70(d)(2)(v) and 601.12(d)(2)(iv), the following change was to be documented in the next annual report: A change within the container closure system for a nonsterile drug product, based upon a showing of equivalency to the approved system under a protocol approved in the application or published in an official compendium.

(Comment 99) One comment said that the proposal, without further explanation, alters the reporting category applicable to changes within the container/closure system for sterile liquid drugs that are made based on a

showing of equivalency to the approved system under a protocol approved in the application or published in an official compendium (for example, the USP). The comment said that under current § 314.70(d)(6), these changes are described in the annual report and do not require FDA prior approval. The comment said that FDA has not provided any rationale for its proposal to require a supplement to be filed in connection with any change within a packaging material for a sterile liquid drug, even in situations in which the change is based on a showing of equivalency to the approved system under a protocol approved in the application or published in an official compendium, and recommended that "nonsterile" be deleted. The comment said that in the same way, it would be unduly burdensome to require FDA prior approval for a change within a container/closure system for a material based on a determination of equivalency made in accordance with a USP monograph that is specifically designed for that purpose. The comment said, for example, the USP chapter for "Polyethylene Terephthalate (PET) Bottles and Polyethylene Terephthalate G (PETG) Bottles" provides standards and tests to characterize PET and PETG bottles "that are interchangeably suitable for packaging liquid oral dosage forms" (USP 25, General Chapter <661> (2002 ed.)). The comment said that FDA is provided with the opportunity to review and comment on USP monographs before they are published in final form; thus, the requirement for an additional FDA prior review of a change made in accordance with USP monograph is unnecessary.

FDA declines to revise the regulation as requested. All container closure systems changes must be supported with data to demonstrate that various characteristics of the drug product and/or container closure system are unchanged or equivalent (e.g., physical, chemical). For a sterile drug product,

however, data must also be provided to support that the sterility assurance level and the maintenance of sterility for the product has not been affected. Sterility of drug products is a fundamental and essential quality attribute of these drugs and is a critical aspect of the safety assessment. FDA would consider an assessment of the effects of a change in a container closure system for a sterile product to be inadequate if it did not include tests and data relating to sterility assurance and maintenance of sterility. FDA considers changes in the container closure system for sterile drug products to be changes that may affect the sterility assurance and/or maintenance of sterility of a drug and, therefore, may have significant potential to affect the safety of the drug. Therefore, FDA has identified this change as one that requires prior approval (see comment 34 of this document).

As stated in the June 1999 proposal, this rulemaking sets out broad, general categories of manufacturing changes, and the agency uses guidance documents to provide FDA's current thinking on the specific changes included in those categories. Through guidance, FDA may identify certain container closure system changes for sterile drug products that can be reported other than by submission of a prior approval supplement. Furthermore, an applicant could submit a comparability protocol that would allow it to implement postapproval changes in sterile container closure systems without a prior approval supplement. FDA notes that, as of 2002, no official compendia has finalized an equivalency protocol for container closure systems for sterile drug products. If such a protocol is published in the future, FDA will consider identifying in a guidance a reporting category other than a prior approval supplement for the compendial protocol if the protocol adequately addresses the appropriate scientific issues.

FDA specifically wishes to address the comment's implication that changes made under the USP monograph for "Polyethylene Terephthalate Bottles and Polyethylene Terephthalate G Bottles" could be submitted in an annual report under this provision. As with any change and as required by the act, the applicant must assess the effects of the change on the identity, strength, quality, purity, and potency of the drug product as these factors may relate to the safety and effectiveness of the product. Moreover, USP <661> states that "the suitability of a specific PET or PETG bottle for use in the dispensing of a particular pharmaceutical liquid oral dosage form must be established by appropriate testing." Testing solely by the standards set in this general chapter would not usually be considered by FDA to be sufficient to assess the effects of the change because the interaction between a specific drug product and specific container and closure system should be assessed.

Under proposed §§ 314.70(d)(2)(vi) and 601.12(d)(2)(iii), the following change was to be documented in the next annual report: An extension of an expiration dating period based upon full shelf life data on full production batches obtained from a protocol approved in the application.

(Comment 100) Many comments recommended changes relating to the phrase "full production batches." A few comments recommended deleting the phrase because this requirement would unnecessarily increase regulatory burden, is unnecessarily restrictive, and/or because applicants should be allowed to use either pilot or production batches to extend an expiration date. One comment further said that pilot batches can be used to support the safety and efficacy of the product and for approval of an NDA expiration date; therefore, pilot batches should be allowed to support an extension of an expiration dating period. Another comment recommended that "full" be

replaced by "production-scale." The comment said that the word "full" may cause confusion, where batch scale for a product may be varied. The comment said that "full" could be interpreted as that only the largest size batch of an approved batch size range could be used to support an extension of an expiration dating period. One comment said that it should be clarified that the batch need not have been sold. One comment said that production lots should be defined in the "definitions" section to include validation/scale-up batches manufactured by the representative production process within a ten-fold batch size for consistency with SUPAC/BACPAC.

FDA has revised §§ 314.70(d)(2)(vi) and 601.12(d)(2)(iii) by replacing the term "full production batch" with "production batch." FDA declines to include a definition of production batch in the regulations. A definition is included in the ICH guidance entitled "Stability Testing of New Drug Substances and Drug Products." FDA considers a production batch to be one made at production scale using production equipment in a production facility as specified in the application. Production scale does not necessarily mean the largest batch size produced, but a batch of a size or within a batch size range that has been approved in the application. The batch need not have been sold, but should be one that is eligible to be sold (e.g., must pass its specification). In certain cases, FDA allows data from pilot batches to be used to support approval of an application. This is consistent with FDA's efforts to reduce the time it takes to bring new drugs to market. Often there are changes when moving from a pilot manufacturing process to a production process. Although these are usually minor in nature and not expected to affect the stability of the product, the definitive data to support an expiration date should be based on production batches; therefore, FDA declines to revise the